Supreme Court, U.S.
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No. 06-1291

In the Supreme Court of the United States

AMGEN INC.,

Petitioner,

v.

HOECHST MARION ROUSSEL, INC. (now known as AVENTIS PHARMACEUTICALS INC.) and TRANSKARYOTIC THERAPIES, INC. (now known as SHIRE HUMAN GENETIC THERAPIES, INC.),

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI APPENDIX VOLUME I OF II

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APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

05-1157

AMGEN INC.,
Plaintiff-Appellee,

v.

HOECHST MARION ROUSSEL, INC.
(now known as Aventis Pharmaceuticals Inc.)
and TRANSKARYOTIC THERAPIES, INC.,
Defendants-Appellants.

DECIDED: August 3, 2006

Before MICHEL, *Chief Judge*, CLEVENGER, *Senior Circuit Judge*, and SCHALL, *Circuit Judge*.

Opinion for the court filed by *Circuit Judge* SCHALL.

Dissenting-in-part opinion [p. 43a, *infra*] filed by *Chief Judge* MICHEL.

SCHALL, *Circuit Judge*.

This is a patent case. Amgen, Inc. ("Amgen") is the owner of U.S. Patent Nos. 5,547,933 ("the '933 patent"), 5,618,698 ("the '698 patent"), 5,621,080 ("the '080 patent"), 5,756,349 ("the '349 patent"), and 5,955,422 ("the '422 patent"). The patents are directed to recombinant deoxyribonucleic acid ("DNA") technology relating to the production of the hormone erythropoietin ("EPO"). All five patents share a common specification and descend from Application No. 06/561,024 ("the '024 application"), filed on December 13, 1983. In April of 1997, Amgen brought a declaratory

judgment action against Hoechst Marion Roussel, Inc. (now known as Aventis Pharmaceuticals Inc.) ("HMR") and Transkaryotic Therapies, Inc. ("TKT") (collectively, "HMR/TKT") in the United States District Court for the District of Massachusetts, alleging that HMR/TKT's Investigational New Drug Application ("INDA") for an EPO product infringed the five patents. In January of 2001, following a *Markman* hearing, summary judgment proceedings, and a bench trial, the district court issued an opinion in which it: (i) construed the disputed claims; (ii) held the patents not unenforceable; (iii) held the asserted claims of the '080, '349, and '422 patents not invalid and infringed with the exception of claim 7 of the '349 patent, which it found not infringed; (iv) held the asserted claims of the '698 patent not infringed; and (v) held the asserted claims of the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 165-66 (D. Mass. 2001) ("*Amgen I*").

In *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) ("*Amgen II*"), we affirmed *in toto* the district court's claim construction. We also affirmed (i) the court's determination that none of the patents at issue is unenforceable by reason of inequitable conduct; (ii) its contingent determination that the asserted claims of the '933 patent are invalid under section 112; (iii) its grant of summary judgment that claim 1 of the '422 patent is infringed; (iv) its determination that the '933, '698, '080, and '349 patents are not anticipated by U.S. Patent No. 4,377,513 ("the Sugimoto patent"); and (iv) its determination that claims 1, 3, 4, and 6 of the '349 patent are infringed. *Id.* at 1320.

However, we vacated (i) the district court's determination that the asserted claims of the '933 patent are not infringed; (ii) its determination that Dr. Eugene Goldwasser's clinical study, described in Dr. Goldwasser's grant application entitled "Erythropoietin: Purification, Properties, Biogenesis"

("the Goldwasser reference"), and the Sugimoto patent do not anticipate claim 1 of the '422 patent; (iii) its determination that the Sugimoto patent does not render claim 1 of the '422 patent obvious; (iv) its determination that claims 2-4 of the '080 patent are not invalid and are infringed under the doctrine of equivalents; (v) its determination that the asserted method claims of the '698 patent are not rendered obvious by the Sugimoto patent and are not infringed; and (vi) its determination that the Sugimoto patent does not render claims 1, 3, 4, 6, and 7 of the '349 patent invalid and that claim 7 of the '349 patent is not infringed. *Id.*

We remanded the case to the district court to do the following: (i) construe the term "therapeutically effective amount" in claim 1 of the '422 patent and then determine whether either the Goldwasser reference or the Sugimoto patent anticipates claim 1 or whether the Sugimoto patent renders claim 1 obvious, *id.* at 1354, 1356, 1358; (ii) determine whether the Sugimoto patent renders claims 2-4 of the '080 patent obvious and whether, as far as claims 2-4 are concerned, Amgen can rebut the presumption of the surrender of equivalents and thus assert infringement of those claims under the doctrine of equivalents, *id.* at 1345, 1358; (iii) determine whether the Sugimoto patent renders claims 4-9 of the '698 patent obvious and whether claims 4-9 are infringed, *id.* at 1357, 1358; and (iv) determine whether the Sugimoto patent renders claims 1, 3, 4, 6, and 7 of the '349 patent obvious and whether claim 7 of the '349 patent is infringed, *id.* at 1357, 1358.

The case is now back before us following proceedings on remand in which the district court construed the term "therapeutically effective amount" in claim 1 of the '422 patent and conducted a further bench trial. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202 (D. Mass. 2004) ("*Amgen III Validity & Literal Infringement Judgment*"); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 287 F.

Supp. 2d 126 (D. Mass. 2003) ("*Amgen III Doctrine of Equivalents Judgment*"). Based upon various findings and rulings, the court entered judgment in favor of Amgen as follows: (i) claim 1 of the '422 patent is not invalid, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 334, 336; (ii) claims 2-4 of the '080 patent are not invalid, *id.* at 336, and Amgen is not estopped from asserting infringement of claims 2-4 under the doctrine of equivalents because it rebutted the presumption of surrender of equivalents, *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 160; (iii) claims 4-9 of the '698 patent are not invalid and are literally infringed, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 336; (iv) claims 1, 3, 4, 6, and 7 of the '349 patent are not rendered obvious by the Sugimoto patent, *id.* at 325, 336, and claim 7 of the '349 patent is literally infringed, *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 336.

On appeal, HMR/TKT challenges all of the above rulings. Our disposition of the appeal is as follows:

(i) Because we hold that the district court erred in its construction of the term "therapeutically effective amount" in claim 1 of the '422 patent, we vacate the judgment of the district court that claim 1 is not invalid. We remand the case to the district court for a determination as to whether the Goldwasser reference anticipates claim 1 under a revised claim construction. (ii) We reverse the judgment of the district court that HMR/TKT's accused product infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We do so because we hold that the district court erred in ruling that Amgen rebutted the presumption that, during prosecution, it surrendered coverage to EPO with a 165-amino acid sequence, which is the sequence of HMR/TKT's product. Because claims 2-4 of the '080 patent are not infringed, it is unnecessary for us to address HMR/TKT's alternative argument by way of an affirmative defense that

claims 2-4 are anticipated by the Goldwasser reference. (iii) We affirm the judgment of the district court that claims 4-9 of the '698 patent are not invalid and are literally infringed. (iv) We affirm the judgment of the district court that claim 7 of the '349 patent is not invalid and is literally infringed. Thus, we affirm-in-part, reverse-in-part, vacate-in-part, and remand.[1]

BACKGROUND

I.

As noted, the patents at issue relate to recombinant DNA technology for the production of EPO. EPO, which is a naturally occurring hormone, stimulates the production of red blood cells in the bone marrow through a process called erythropoiesis. Thus, the production of EPO is useful in treating blood disorders characterized by low hematocrit, which is a low ratio of red blood cells to total blood cells. The production of EPO in usable amounts was made possible by Amgen's team led by Dr. Fu-Kuen Lin, who first successfully identified the EPO DNA sequence. *See* '422 patent, col. 20, ll. 28-33. Amgen markets and sells its EPO product under the brand name "Epogen."

DNA is the genetic material of all living things.[2] *Id.* col. 1, ll. 28-29. DNA is composed of a series of subunits, called nucleotides, that are linked together to form a linear polymeric form—a strand. *Id.* col. 1, ll. 33-35. Each nucleotide contains one of four nitrogen-containing ring compounds, called bases. The bases fall into two categories: pyrimidines,

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[1] Even though we do not agree with all of the district court's rulings in this case, we note the court's careful and thorough opinions in both *Amgen III Validity & Literal Infringement Judgment* and *Amgen III Doctrine of Equivalents Judgment.*

[2] The basics of recombinant DNA technology are set forth in *Amgen I* and, to a lesser extent, in *Amgen II*. We repeat here only the points necessary for an understanding of the issues presented in this appeal.

which include cytosine ("C") and thymine ("T"), and purines, which include adenine ("A") and guanine ("G"). *Id.* col. 1, ll. 35-46; James D. Watson et al., *Molecular Biology of the Gene* 98 (5th ed. 2004); Bruce Alberts et al., *Molecular Biology of the Cell* 63, 120 (4th ed. 2002). The sequence of A, T, G, and Cs on a strand of DNA forms what is known as a "DNA sequence." DNA is double-stranded, such that two complimentary strands are linked together. '422 patent, col. 1, ll. 35-42.

Genetic information is expressed through the production of proteins, which are molecules containing long chains of amino acids. Alberts, *supra*, at 129. Ribonucleic acid ("RNA") determines the composition of proteins. Watson, *supra*, at 31; *see also* Alberts, *supra*, at 301. During a process called transcription, DNA is used to make messenger RNA ("mRNA") with the sequence corresponding to the DNA sequence of A, T, G, and Cs coding for a particular gene.[3] '422 patent, col. 1, ll. 42-43, 49-51. Transcription of the gene is prompted by a promoter, a sequence of DNA that initiates transcription. *Id.* col. 2, ll. 4-6. The promoter is typically located upstream of the gene to be transcribed.[4] *Id.* After transcription is completed, the mRNA non-coding sequences, called introns, are spliced out and the mRNA coding sequences, called exons, are spliced together. The mRNA sequence is then translated by ribosomes to form a protein

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[3] As the name "messenger" implies, mRNA transcripts are intermediates in the process of protein synthesis. Transcription of mRNA from DNA is completed in the nucleus of the cell. After it undergoes additional processing in the cell's nucleus, the complete mRNA is exported to the cell's cytoplasm, where it guides the synthesis of proteins. *See* Alberts, *supra* at 304-05, 327-28.

[4] "Upstream" refers to the location of a particular segment of the genetic sequence on a strand of DNA in relation to a particular gene. For example, if a segment is "upstream" of a particular gene and transcription proceeds in a completely linear order along the DNA sequence, then the segment will be transcribed before the gene.

composed of amino acids. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 145.

The common specification of Amgen's patents describes how Dr. Lin combined his discovery of the DNA sequence for EPO with recombinant DNA technology to make EPO-producing cells. In order to create these EPO-producing cells, Dr. Lin made an expression vector carrying the EPO DNA sequence he had discovered. '422 patent, col. 11, ll. 1-10. An expression vector is a circular piece of DNA on which a desired gene may be coded. *See id.* Figs. 2-4, col. 2, ll. 36-54. In addition to the desired gene, an expression vector may also contain a marker and a promoter site. *See id.* col. 3, ll. 35-37, col. 25, ll. 33-36. The expression vector incorporates itself into a host cell's genetic code. The promoter then triggers the host cell to transcribe mRNA corresponding to the genetic code encoded on the vector. *See id.* col. 2, ll. 30-35. This mRNA is then translated into a protein by the host cell. *Id.* The marker in the expression vector enables scientists to identify the cells that successfully incorporated the desired gene. *Id.* col. 25, ll. 64-66. The DNA inserted into the genetic code of the host cell through the expression vector is characterized as exogenous DNA because it is not "native" to the host cell. Genetic recombination using exogenous DNA is referred to as heterologous recombination. *Id.* col. 1, l. 53-col. 2, l. 3.

The expression vector described in Example 10 of the common specification of Amgen's patents contains Dr. Lin's EPO DNA sequence, a selectable dihydrofolate ("DHFR") marker, and a promoter 44 base pairs upstream of the EPO DNA sequence. *Id.* col. 24, l. 17, col. 25, 36-40. When exposed to Chinese hamster ovary ("CHO") cells, Dr. Lin's expression vectors integrate themselves into the DNA of the host CHO cells. *Id.* col. 25, ll. 58-66. The general disclosures in the background section of the '422 patent describe how promoters, like the one used in Example 10, prompt host cells

to transcribe mRNA corresponding to exogenous genes such as the EPO and DHFR genes in Example 10. *See id.* col. 1, ll. 53-56, col. 25, ll. 64-66. In the invention of the five patents, prior to production of a protein from the mRNA with the sequence coding for EPO, the mRNA sequence is spliced to remove introns and to connect exons. After splicing, the mRNA is translated into the 166-amino acid protein shown in Figure 6 of the common specification of the patents.

Prior to secretion from the cell, the 166-amino acid EPO protein undergoes cleaving. In this process, the final amino acid in the sequence shown in Figure 6 of the '422 patent, arginine, is cleaved off, leaving a 165-amino acid protein. This 165-amino acid protein is then secreted as mature human EPO by the cell.

II.

HMR and TKT collaborated to develop a drug known as HMR4396. HMR4396 consists of human EPO produced from TKT's R223 cell line grown in culture. *Amgen I*, 126 F. Supp. 2d at 98. The R223 cell line produces human EPO through the use of a viral promoter that prompts transcription of the human EPO gene. In order to create the R223 cell line, HMR/TKT transfected human tumor cells with the viral promoter. This viral promoter is located far upstream of the EPO gene in the R223 cells. Because the viral promoter is not "native" to the human tumor cells, the R223 promoter is considered exogenous DNA. However, the R223 cells are described as using homologous or endogenous recombination because the human EPO gene that the viral promoter controls is "native" to the cells.

III.

Amgen filed suit for a declaratory judgment that HMR/TKT's HMR4396 infringed the '933 patent, the '698 patent, the '080 patent, the '349 patent, and the '422 patent. Amgen alleged infringement of claims 1, 2, and 9 of the '933 patent,

claims 4-9 of the '698 patent, claims 2-4 of the '080 patent, claims 1, 3, 4, 6, and 7 of the'349 patent, and claim 1 of the '422 patent. *See Amgen I*, 126 F. Supp. 2d at 96-98. The case proceeded as outlined above and is again before us on appeal. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

On this appeal, we are presented with issues relating to the '422, '080, '698, and '349 patents.[5] We begin with the '422 patent.

I.

The '422 Patent

Claim 1 is the only claim of the '422 patent at issue in the present case. Claim 1 provides:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture.

'422 patent, col. 38, ll. 36-41.

HMR4396 already has been found to infringe claim 1 of the '422 patent. *See Amgen II*, 314 F.3d at 1320. In our remand instructions in *Amgen II*, we instructed the district court to construe the limitation "therapeutically effective amount" in claim 1 and then determine whether the Goldwasser reference or the Sugimoto patent anticipated claim 1 or whether the Sugimoto patent rendered claim 1 obvious.

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[5] As noted above, in *Amgen II*, we affirmed the ruling of the district court in *Amgen I* that claims 1, 2, and 9 of the '933 patent are invalid. *Amgen II*, 314 F.3d at 1342.

A.

Claim Construction

On remand, the district court construed "therapeutically effective amount" in claim 1 of the '422 patent to require that the claimed EPO increase hematocrit *and* also be useful in healing or curing the class of patients listed at column 33, lines 22-28 of the specification of the '422 patent:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (see, Eschbach, et al., supra) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

Amgen III Validity & Literal Infringement Judgment, 339 F. Supp. 2d at 245-46. In arriving at this construction, the district court focused on the portion of the specification of the

'422 patent found at column 33, lines 11-28.[6] *Id.* at 232-36. The court also pointed to statements in the prosecution history asserting that the claimed invention of recombinant human EPO could be used to treat anemia and other similar disorders. *Id.* at 238-42.

On appeal, HMR/TKT contends that the district court erred in construing the term "therapeutically effective" in claim 1 of the '422 patent by requiring that EPO increase hematocrit. HMR/TKT argues that the court incorrectly read the specification as limiting the scope of claim 1 to products that increase hematocrit. HMR/TKT urges that "therapeutically effective amount" means "an amount that elicits any of the biological effects listed in the specification." Under this construction, HMR/TKT asserts, claim 1 is anticipated by the Goldwasser reference.

Amgen responds that the district court correctly interpreted the specification to mean that "when a 'therapeutically effective amount' of EPO is used . . . it produces an increase in hematocrit—along with any or all of the biological affects [sic] previously attributed to natural EPO." Appellee's Br. 21 (quoting *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 234). Amgen points out that although the passage at column 33, lines 11-22 does not actually use the term "therapeutically effective," other passages do, in fact, use the term. For example, at column 33, lines 43-50, Amgen notes, the patent actually uses the words "therapeutically effective" before explaining the required dosages for patients. According to Amgen, this indicates that "therapeutically effective" amounts are those related to healing or curing

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[6] The district court's claim construction references passages of the '933 patent found at column 33, lines 24-28 and column 33, lines 31-36. *Id.* at 214, 236, 245. The '422 patent contains identical passages at column 33, lines 16-20 and column 33, lines 23-28 respectively. These passages are part of a larger portion of the specification that runs from column 33, lines 11-28.

disease. Amgen also directs our attention to the portion of the specification found at column 33, lines 22-28. This passage states, "Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions . . . and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like." According to Amgen, only amounts of EPO producing effects—particularly increased hematocrit—that counteract these anemia-like diseases are "therapeutically effective." Amgen buttresses this argument with citations to the prosecution history where the patentee recounts the benefits of the claimed invention over prior art in treating disease.

The district court's claim construction is a matter of law, which we review de novo. *Cybor Corp. v. FAS Techs.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc). In *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), we stated that claim construction must begin with the words of the claims themselves. *Id.* at 1312. A claim term has "the meaning that the term would have to a person of ordinary skill in the art. . . ." *Id.* at 1313. This meaning is ascertained "in the context of the entire patent, including the specification." *Id.* In particular, we stated in *Phillips* that "we must look at the ordinary meaning in the context of the written description and the prosecution history." *Id.* (quoting *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005)). When dealing with technical terms, we noted, a court should look to "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)).

Using *Phillips* as a guide, we turn first to the language of the claims. Neither the language of claim 1, nor the language of claim 2, of the '422 patent offer any guidance as to the meaning of "therapeutically effective."[7] However, several passages of the specification shed light on the meaning of the term. In particular, the text found at column 33, lines 11-22 states:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin *therapy procedures* practiced on mammals, including humans, to develop *any or all* of the *effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects* (such as plasma iron turnover effects and marrow transit time effects), *erythrocyte mass changes, stimulation of hemoglobin C synthesis* (see, Eschbach, et al., supra) *and, as indicated in Example 10, increasing hematocrit levels in mammals.*

'422 patent, col. 33, ll. 11-22 (emphases added). This language indicates that the claimed invention is used in "therapy" to produce "any or all" of the following "effects": stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin, and increasing hematocrit levels. Thus, increasing hematocrit is only one of the biological effects produced by the claimed invention. Accordingly, we agree with HMR/TKT that the district court misinterpreted this passage when it read it as limiting the claimed invention to

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[7] Claim 2 is an independent claim, which provides: "A pharmaceutically-acceptable preparation containing a therapeutically effective amount of erythropoietin wherein human serum albumin is mixed with said erythropoietin." '422 patent, col. 38, ll. 42-44.

products with "any or all" of the first four listed effects ascribed in vivo to EPO *and also* an increase in hematocrit.

Further, in the August 2, 1993 office action response, the patentee cited the above language of the specification and then stated, "It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be *therapeutically effective.*" (emphasis added). Thus, the patentee interpreted the passage at column 33, lines 11-22 of the specification as listing the therapeutic effects of the invention disclosed in the '422 patent. We think the district court made an artificial distinction between the first four effects listed in column 33, lines 11-22, stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, and stimulation of hemoglobin, and the fifth effect, an increase in hematocrit. The specification lists all five effects after stating that "any or all" of them may be an effect of therapy with the claimed invention. Thus, this section of the specification supports the construction that the '422 patent encompasses a pharmaceutical composition which produces "any or all" of the five listed effects.

As seen, the district court also determined that the specification indicates that the invention is limited to products that are "therapeutically effective" with respect to patients with anemia-like disorders, such as those listed at column 33, lines 22-28 of the '422 patent. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 235-36, 245-46. For this determination, the court relied on a passage that recites several diseases that may be treated by the claimed invention. The passage begins, "Included within the class of humans treatable with products of the invention . . . ." '422 patent, col. 33, ll. 22-28. However, this passage does not state that the claims encompass *only* products that treat such patients. Rather, by using the non-limiting word "included," it

suggests some persons, but not all persons, who may benefit from the invention.

Moreover, an additional section of the specification states, "It is noteworthy that the absence of in vivo activity for any one or more of the 'EPO products' of the invention is not wholly preclusive of therapeutic utility (see Weiland, et al., supra). . . ." *Id.* col. 36, ll. 9-12. We think the message of this passage is that "therapeutic utility" is not limited to products with "in vivo" effects. Thus, "therapeutic utility" is not dependent on the product having an effect in a living being, such as curing disease. Although this passage relates to a different EPO product than the one disclosed in claim 1 of the '422 patent, we think it illustrates the broad meaning of "therapeutic utility" used throughout the '422 patent. It shows that the patentee did not use the word "therapy" in order to limit the scope of the '422 patent to only EPO that cured disease. Thus, products that are not necessarily effective in actually curing disease in humans are encompassed by claim 1 of the '422 patent. Based on a reading of the claims in light of the specification, it appears that the patentee used the words "therapeutically effective" in order to broadly claim a pharmaceutical composition with a wide range of effects. Those effects do not *necessarily* include curing disease in humans.

During the prosecution of the '422 patent, in an office action response filed October 23, 1997, the patentee noted that recombinant EPO, like that found in the claimed invention, "is the first therapeutic product which can be used to effectively treat hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts." In our view, this statement merely lists some of the uses of the invention, without restricting the scope of the invention.

In sum, we disagree with the district court's claim construction to the extent that it limits the scope of claim 1 of the

'422 patent to EPO products that have one of the in vivo effects listed at column 33, lines 16-20 *and that also* increase hematocrit. We also disagree with the district court's conclusion that claim 1 of the '422 patent is limited to EPO products that may be used to treat patients with the disorders listed at column 33, lines 22-28 of the '422 patent's specification. On remand, the district court should utilize the following revised construction of "therapeutically effective:"

> A therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals.

B.

Anticipation—The Goldwasser Reference

Based on its claim construction, the district court found in *Amgen III Validity & Literal Infringement Judgment* that the Goldwasser reference did not anticipate claim 1 of the '422 patent because Dr. Goldwasser's study was not effective in healing or curing. 339 F. Supp. 2d at 327. The parties dispute whether the Goldwasser reference anticipates claim 1 of the '422 patent under a revised claim construction. The purpose of the Goldwasser study was to examine EPO and its effects on erythropoiesis. Dr. Goldwasser acknowledged that mass production of EPO from recombinant DNA was not yet possible. Therefore, Dr. Goldwasser utilized EPO isolated from urine in an attempt to discover the chemistry and mode of action of EPO. In one portion of his study, Dr. Goldwasser performed a "very small clinical trial" using pure urinary

EPO ("uEPO"). The uEPO was administered to three anemic patients. Two patients received injections of 520 units twice daily for ten days. The third patient received a 1000 unit injection every 2-3 days for three weeks. In his 1984 grant application, Dr. Goldwasser described the results of the clinical study as follows:

> There was no significant change in hematocrit in any patient; each patient, however[,] showed an increase in reticulocyte count, with peaks at 9, 10[,] and 11 days. The first two patients had increased erythroid cells in the marrow and an increased plasma iron clearance rate. One of the first two patients showed an increase in red cell mass. These fragmentary data, need to be reinforced with more extensive and extended studies but they show that epo can have a physiological effect in this type of anemia.

In *Amgen I*, the district court noted that Dr. Goldwasser testified that this "abortive, three-patient trial was a failure." 126 F. Supp. 2d at 112.

The district court found that the Goldwasser reference did not anticipate claim 1 of the '422 patent because none of the effects listed in Dr. Goldwasser's study included healing or curing within the court's construction of "therapeutically effective." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 327-34. HMR/TKT argues that under a revised construction of "therapeutically effective" that broadens the scope of claim 1 to encompass EPO that "elicits any of the biological effects listed in the specification [at column 33, lines 16-22]," Dr. Goldwasser's study anticipates. Amgen counters that even under a broader construction of "therapeutically effective," Dr. Goldwasser's study does not anticipate claim 1 of the '422 patent because its recombinant EPO ("rEPO") product differs in structure and function from the uEPO utilized in Dr. Goldwasser's study. Amgen argues that a remand is not necessary because

HMR/TKT admitted in its petition for a panel rehearing and rehearing en banc following *Amgen II* that the rEPO disclosed in claim 1 of the '422 patent differs in structure from naturally occurring uEPO.

Anticipation under 35 U.S.C. § 102 is a question of fact, which we review for clear error after a bench trial. *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369 (Fed. Cir. 2003); *Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1369 (Fed. Cir. 2004). The district court's factual findings on anticipation are clearly erroneous when "'although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed.'" *Merck & Co*, 347 F.3d at 1369 (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)). A prior art reference anticipates a patent if it discloses all the limitations of the claimed invention. *Oney v. Ratliff*, 182 F.3d 893, 895 (Fed. Cir. 1999).

The district court's findings of fact on anticipation centered on whether the effects produced on patients in Dr. Goldwasser's study resulted in healing or curing. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 327. Under our construction of "therapeutically effective," however, the district court's findings of fact as to "healing or curing," while relevant, do not end the anticipation inquiry. Additional findings of fact are necessary to determine whether the Goldwasser study anticipates under our new construction of "therapeutically effective." When findings of fact are necessary under a revised claim construction, it is appropriate for us to remand to the district court. *See Seachange Int'l, Inc. v. C-Cor Inc.*, 413 F.3d 1361, 1381 (Fed. Cir. 2005) (remanding for the district court to consider anticipation after revising the claim construction). On remand, the district court should make findings of fact as to

whether the Goldwasser reference meets the "therapeutically effective" limitation under our construction.[8]

C.

Anticipation—The Sugimoto Patent

The Sugimoto patent, filed August 10, 1981, discloses a method for creating EPO-producing cells by creating hybrid cells from lymphoblastoids[9] and kidney tumor cells. The Sugimoto patent suggests using recombinant techniques to introduce the EPO genes from a human kidney tumor cell into human lymphoblastoids. Sugimoto patent, col. 1, l. 55–col. 2, l. 11. The patent involves in vivo production of EPO in which human lymphoblastoid cells capable of producing EPO are transferred to an animal body. The Sugimoto patent explains that the EPO produced by the animal according to this technique is then "collected easily by purification and separation techniques using conventional procedures . . . ." *Id.* col. 3, ll. 51-53.

In *Amgen I*, the district court found that the Sugimoto patent did not anticipate claim 1 of the '422 patent because it was not enabled. 126 F. Supp. 2d at 109. The court considered the testimony of Amgen's expert, Dr. Allan Erslev, who stated that the Sugimoto procedure was "very complex." *Id.* at 108. Dr. Erslev stated that no one had used the Sugimoto process prior to 1984, even though it would have been highly profitable if successful. *Id.* After recounting Dr. Erslev's testimony, the court discounted HMR/TKT's arguments. *Id.* HMR/TKT had put Dr. Michael

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[8] If, on remand, the district court finds that the Goldwasser reference contains the "therapeutically effective" limitation, it must then determine whether the uEPO meets the other limitations of claim 1 of the '422 patent.

[9] Lymphoblastoids are cells that are typically isolated from patients with leukemia, which is a cancer of the blood. *Amgen I*, 126 F. Supp. 2d at 106.

Heartlein on the stand. By attempting to replicate the Sugimoto process, Dr. Heartlein produced cells that generated six times as much EPO as their parent cells. *Id.* at 108-09. The court found that Dr. Heartlein's experiments were not sufficient to show enablement, however, because Dr. Heartlein followed a different procedure than the one disclosed in the Sugimoto patent. First, Dr. Heartlein used an in vitro technique rather than an in vivo technique like that disclosed in the Sugimoto patent. *Id.* at 109. Second, the district court found that Dr. Heartlein used different starting materials than the Sugimoto patent because he could not obtain kidney tumor cells like those disclosed in the Sugimoto patent. *Id.* Based on the foregoing, the district court found that HMR/TKT had failed to demonstrate that the Sugimoto patent was enabled by clear and convincing evidence. *Id.* at 108–09.

On appeal, we ruled in *Amgen II* that the district court had erred in placing the burden of proving enablement on HMR/TKT. *Id.* at 1357. We indicated that the Sugimoto patent should have been presumed enabled and that Amgen should have had the burden of proving otherwise. *Id.* at 1355.

On remand, the district court affirmed its previous holding of non-enablement, finding that "Amgen has shown by a preponderance of the evidence that Sugimoto is not enabled . . . ." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 307. The court based its conclusion that the Sugimoto patent was not enabled on three findings. First, the court noted that the Sugimoto patent did not disclose the starting materials necessary to repeat the process it describes. *Id.* at 307-09. The Sugimoto patent required the use of kidney tumor cells, but the inventor neither deposited these cells publicly nor did he disclose them so that a person of ordinary skill in the art could procure them. *Id.* at 307. Second, the court found that the Sugimoto patent was not enabled because it did not teach a person of ordinary skill in

the art how to select EPO-producing hybrid cells. The court based its finding largely on the testimony of Dr. Howard Green, a cell biologist with over forty years of experience, who stated that although methods for selecting hybrids were available at the time the Sugimoto patent was filed, they were inconsistently successful and required undue experimentation to produce results. *Id.* at 309. Third, the court found that the Sugimoto patent did not enable a method for purifying EPO even though the Sugimoto patent claimed to teach how to produce purified EPO. *Id.* at 311-12. The court found support for this finding in the testimony of Dr. Green, *id.* at 311, as well as in evidence that the Sugimoto patent's disclosure still had not been put into practice years after it issued in March of 1983, *id.* at 312. In addition, in connection with all three findings, the court noted that Dr. Heartlein had failed to duplicate the Sugimoto starting materials, selection methods, or purification techniques when using the disclosure of the Sugimoto patent. *Id.* at 307-08, 311-12.

HMR/TKT makes several arguments for reversing the district court's finding of non-enablement. With regard to the district court's finding that the cells necessary for the Sugimoto procedure were not adequately disclosed or deposited, HMR/TKT urges that the description of the starting materials in the Sugimoto patent was sufficient despite the fact that the cells were not deposited. HMR/TKT notes that the Patent and Trademark Office found that there was an adequate written description and that a person of ordinary skill in the art would have understood the disclosure. HMR/TKT asserts that the district court's use of Dr. Heartlein's experiments as proof of non-enablement was flawed because the district court previously found in *Amgen I* that Dr. Heartlein did not follow the Sugimoto patent's disclosure.

Amgen defends the district court's decision on remand by arguing that the district court correctly identified deficiencies in the Sugimoto patent's disclosure. First, Amgen argues that

the lack of starting materials is illustrated by both Amgen's and Dr. Heartlein's inability to obtain the kidney tumor cells described in the Sugimoto patent. Amgen also notes that EPO-producing cells prior to Dr. Lin's invention were "poor producers." In addition, Amgen argues that the district court correctly found that the Sugimoto patent was not enabled based on the lack of disclosure of a method for hybrid cell selection or purification.

In order to anticipate, a prior art reference must not only disclose all of the limitations of the claimed invention, but also be enabled. *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). A reference is enabled when its disclosures are sufficient to allow one of skill in the art to make and use the claimed invention. *Id.* (quoting *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001)). Like a patent, a prior art reference is enabled even if some "routine experimentation is required in order to practice a claimed invention, but . . . such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). When considering whether or not a prior art reference requires "undue experimentation" we look at the reference from the perspective of a person of ordinary skill in the art. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988).

We established in *Amgen II* that when a piece of prior art is a patent, like the Sugimoto patent, there is a presumption of enablement. 314 F.3d at 1355. The patentee, Amgen, must present persuasive evidence of non-enablement to overcome this presumption. *Id.* As seen, in *Amgen II*, we vacated and remanded the finding of non-enablement with regard to claim 1 of the '422 patent. On remand, the district court found that Amgen had met its burden of proving by a preponderance of the evidence that the Sugimoto patent was not enabled. 339 F. Supp. 2d at 306. We review the district court's ultimate determination of enablement de novo while the underlying

factual inquiries made by the district court are reviewed for clear error. *Enzo Biochem*, 188 F.3d at 1369.

The district court's factual finding that the Sugimoto patent did not adequately disclose the starting materials was not clearly erroneous. The court based its conclusion on the testimony of several scientists with experience in the field of erythropoeisis, including Dr. Green, Dr. Lin, and Dr. Harvey Lodish, a research biologist at the Whitehead Institute and the Massachusetts Institute of Technology. Dr. Green testified that Dr. Heartlein, who attempted to duplicate the Sugimoto disclosure, searched "for a long time and in many different ways" to find a suitable cell line and finally settled on a liver tumor cell line—not a kidney tumor cell line like Sugimoto's. Dr. Lin testified that he had searched extensively for an EPO-producing cell line during his research, but never acquired a EPO-producing kidney tumor cell line. Dr. Lodish stated that the Sugimoto patent failed to demonstrate that the kidney tumor cells disclosed in the patent actually produced EPO. In addition, Amgen presented evidence that it failed to locate any kidney tumor cells, like those described in the Sugimoto patent, despite repeated efforts to do so. At the same time, we do not see clear error in the court's finding that Dr. Heartlein's non-conforming experiments show that a person of ordinary skill in the art would not be able to obtain the required kidney tumor cells based on the Sugimoto patent's disclosures. The failure of Dr. Heartlein to obtain the cells disclosed by the Sugimoto patent and the expert testimony of Drs. Green, Lin, and Lodish support this finding. Further, Sugimoto did not deposit the EPO-producing kidney tumor cells described in the Sugimoto patent. In sum, the Sugimoto patent was not enabled due to the patentee's failure to adequately describe how to derive the starting materials or deposit the cells. *See In re Wands*, 858 F.2d at 735 ("Where an invention depends on the use of living materials such as microorganisms or cultured cells, it may be impossible to enable the public to make the invention (i.e., to obtain these

living materials) solely by means of a written disclosure."). Because we discern no clear error in the district court's finding that the Sugimoto patent's failure to disclose or deposit the starting materials necessary to produce EPO rendered the patent not enabled, it is unnecessary for us to address Amgen's arguments that the Sugimoto patent also did not teach how to select hybrid cells and that the Sugimoto patent did not disclose a means for purifying EPO.

D.

Obviousness—The Sugimoto Patent

The district court held in *Amgen I* that the Sugimoto patent did not render claim 1 of the '422 patent obvious because the Sugimoto patent was not enabled. 126 F. Supp. 2d at 114 & n.29. In *Amgen II* we vacated this finding and remanded because non-enablement does not preclude a finding of obviousness. 314 F.3d at 1357. On remand, in *Amgen III Validity & Literal Infringement Judgment*, the district court again concluded that the Sugimoto patent did not render claim 1 of the '422 patent obvious. In reaching this conclusion, the court considered the scope and content of the prior art, differences between the claimed invention and the prior art, the level of ordinary skill in the art, and reasonable expectation of success. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 316-19. The court also placed emphasis on the "objective indicia of non-obviousness," or "secondary considerations." *Id.* at 314, 319. Specifically, the court found that there had been a long-felt, but unmet need for EPO-producing cells prior to Dr. Lin's discovery. *Id.* at 319. Thus, the district court concluded that HMR/TKT "failed to persuade the Court by clear and convincing evidence that the asserted claims of [Amgen's patents] were obvious in light of Sugimoto." *Id.* at 325. HMR/TKT appeals the district court's ruling.

We have considered the various arguments made by HMR/TKT on the obviousness issue. Having done so, we see no reason to disturb the ruling of the district court that HMR/TKT failed to establish that claim 1 of the '422 patent was obvious in view of the Sugimoto patent.

II.

The '080 Patent

As seen, in *Amgen III Doctrine of Equivalents Judgment*, the district court ruled that claims 2-4 of the '080 patent were not invalid and that Amgen was not estopped from asserting infringement under the doctrine of equivalents. 287 F. Supp. 2d at 160. Accordingly, the court reinstated its vacated finding in *Amgen I* that claims 2-4 of the '080 patent were infringed under the doctrine of equivalents by HMR/TKT's HMR4396 product. *Id.* The only issue before us on appeal is infringement under the doctrine of equivalents. Claims 2-4 provide:

> 2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.
>
> 3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.
>
> 4. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 1, 2 or 3.

'080 patent, col. 38, ll. 39-53. Claims 2-4 of the '080 patent each contain the limitation that the "erythropoietin glyco-

protein comprises the mature erythropoietin amino acid sequence of FIG. 6." The sequence shown in Figure 6 of the '080 patent has a DNA sequence coding for 166 amino acids. However, as noted above, mature human EPO actually contains 165 amino acids, because the 166th amino acid, arginine, is cleaved off prior to the EPO's secretion from the cell. The question before us is whether prosecution history estoppel bars Amgen from claiming that claims 2-4 of the '080 patent encompass EPO with 165 amino acids under the doctrine of equivalents. This is critical because HMR/TKT's EPO product, HMR4396, has only 165 amino acids. *Id.* at 129.

A.

The application that resulted in the '080 patent was filed on June 6, 1995 as Application No. 08/468,556 ("the '556 application"). The '556 application, which contained 60 claims, was a continuation-in-part of the '024 application. In the first preliminary amendment of the '556 application, the patentee cancelled claims 1-60 and added claims 61-67. Of the seven new claims added by amendment, claims 61-64 comprised the only independent product claims. Proposed claims 61-64 provided as follows:

> 61. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having glycosylation which differs from that of human urinary erythropoietin.
>
> 62. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE.
>
> 63. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources and free of other human proteins.

64. The in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and

(b) isolating said erythropoietin product therefrom.

The patentee made a second preliminary amendment to the '556 application on December 20, 1995. In the second preliminary amendment, claims 61-63 were cancelled, claim 64 was amended, and a new claim, claim 68, was added. The amended version of claim 64 provided as follows:

64. The non-naturally occurring in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complimentary strands; and

(b) isolating said erythropoietin product therefrom.

Claim 68, which was added in the second preliminary amendment, provided as follows:

68. A non-naturally occurring erythropoietin product of the process comprising the steps of:

a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and

b) isolating an erythropoietin product therefrom.

In the third and final amendment made to the '556 application for the '080 patent, the patentee cancelled claims 64 through 68 and added claims 69-75. Claims 70-72, which issued as claims 2-4 of the '080 patent, provided as follows:

70. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and is not isolated from human urine.

71. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6.

72. A pharmaceutical composition comprising a therapeutically effective amount [of] an erythropoietin glycoprotein product according to claim 69, 70 or 71.

As seen, after the first preliminary amendment, the claims of the '556 application broadly encompassed an isolated human EPO product. The application claimed an EPO product made using the human EPO DNA sequence set out in Figure 6 or the monkey EPO DNA sequence set out in Figure 5. With the second preliminary amendment, the patentee added claim 68, which claimed an EPO product made using the amino acid sequence for EPO set out in Figure 6 "or a

fragment thereof." With the third preliminary amendment, the patentee removed all references to non-human monkey EPO and also deleted claims for an EPO product made using "a fragment" of the amino acid sequence of Figure 6. Instead, as of the third preliminary amendment, the '556 application claimed only a human EPO product having the complete amino acid sequence of Figure 6.

B.

In *Amgen I*, the district court found that the amendments to the '556 application were made to preempt a double-patenting rejection based on claim 1 of the '933 patent.[10] 126 F. Supp. 2d at 135. The district court held that an amendment made to avoid a double-patenting rejection is not an amendment related to patentability. *Id.* at 136. Therefore, the court held that Amgen was not estopped from claiming that EPO with a 165-amino acid sequence infringed the asserted claims of the '080 patent under the doctrine of equivalents. *Id.*

In *Amgen II*, citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740-41 (2002) ("*Festo II*"), we vacated the district court's finding and held instead that Amgen's double-patenting amendment was an amendment related to patentability that gave rise to prosecution history estoppel. 314 F.3d at 1345. We vacated the district court's finding of infringement of the '080 patent under the doctrine of equivalents and remanded for "an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel." *Id.* These "narrow ways" were first set forth in

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[10] Claim 1 of the '933 patent provides:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22.

Festo II. They are (i) showing that an equivalent was unforeseeable; (ii) demonstrating that the purpose for an amendment was merely tangential to the alleged equivalent; or (iii) establishing "some other reason" that the patentee could not have reasonably been expected to have described the alleged equivalent. 535 U.S. at 740-41.

On remand, in *Amgen III Doctrine of Equivalents Judgment*, the district court evaluated whether any one of the three grounds for rebutting the *Festo* presumption of estoppel had been demonstrated by Amgen. 287 F. Supp. 2d at 147-59. The court determined that Amgen had failed to show that a 165-amino acid EPO was unforeseeable at the time of the third preliminary amendment. *Id.* at 149. However, the court determined that Amgen had succeeded in showing that the third preliminary amendment, which restricted the literal scope of the '080 patent to EPO having the complete amino acid sequence shown in Figure 6, was added only to limit the '080 patent to human EPO products. *Id.* at 152. The court found that the third preliminary amendment was therefore no more than tangentially related to the 165-amino acid equivalent. *Id.* at 154. The court based this finding on the prosecution history, noting that "the chronology and language of the amendments support Amgen's position that it added the amendment in question (the third amendment) to distinguish the '080 patent from the '933 patent on the basis that the '080 was limited to *human* EPO." *Id.* at 152 (emphasis in original). The human EPO limitation thus was merely tangential, the district court found, to the 165-amino acid equivalent. The court buttressed its finding of tangentiality with a "reasonable inference" that the amendment was not made with the intention of surrendering equivalents because, as of December of 1996, when the third preliminary amendment was made, the Patent and Trademark Office and Amgen both were aware that mature EPO had 165 amino acids. *Id.* at 153.

Although the district court found that the *Festo* presumption was rebutted because the amendment limiting the claims of the '080 patent to EPO with the amino acid sequence of Figure 6 was tangential to EPO having a 165-amino acid sequence, it set forth an alternate rationale based on the "some other reason" language in *Festo II*. The court looked to both extrinsic and intrinsic evidence suggesting that the drafter of the amendment, as well as those of ordinary skill in the art, would have considered the amendment to cover all human EPO, regardless of whether or not the EPO had 165 or 166 amino acids. *Id.* at 157. In essence, the court construed the claims based on the extrinsic record (with support from the intrinsic record). *Id.* The court reasoned that this evidence reflected a "shortcoming[ ] of language" or "linguistic" limitation, which were mentioned in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1372 (Fed. Cir. 2003) (en banc) ("*Festo III*"), as possible reasons for rebuttal of the Festo presumption. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 159. The court then found that those equivalents encompassed by this construction were not surrendered, relying on the "some other reason" exception to the *Festo* presumption of surrender of equivalents. *Id.*

HMR/TKT argues on appeal that the district court erred in finding that Amgen's third preliminary amendment was merely tangential to the equivalent EPO having a 165-amino acid sequence. It contends that if the patentee had intended solely to limit the scope of claims 2-4 of the '080 patent to *human* EPO, the patentee would have used the word "human" to describe the EPO. Instead, according to HMR/TKT, the third preliminary amendment uses the word "mature," while both of the previous amendments used the word "human" to describe the EPO claimed. HMR/TKT urges that the district court also erred by finding that Amgen rebutted the *Festo* presumption based on "some other reason." HMR/TKT argues that Amgen amended the claims of the '080 patent to

include only a 166-amino acid EPO out of fear of a new matter rejection, which does not fall under *Festo*'s "some other reason" criterion.

Amgen counters that the district court was correct in its conclusion because the purpose of the third preliminary amendment was to distinguish the '080 patent, which encompasses only *human* EPO, from claim 1 of the '933 patent, which encompasses both human and animal EPO. In support of its argument, Amgen recites its remarks during prosecution "that claims 69, 70, and 71 [currently claims 2-4 of the '080 patent] all differ in scope from glycoprotein claim 1 of U.S. 5,547,933 in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6. Claim 69 [currently claim 1 of the '080 patent] (like ['933] glycoprotein claim 1) recites carbohydrate differences in comparison to human urinary [EPO] and claim 70 [currently claim 2 of the '080 patent] recites a negative limitation with respect to isolation from human urine." (footnote omitted). Based on the foregoing statement in the patentee's remarks accompanying the third preliminary amendment, Amgen contends that the amendment was meant to distinguish Amgen's EPO from naturally-occurring EPO through differences in glycosylation, or "carbohydrate differences." Thus, Amgen argues that the mention of the EPO sequence of Figure 6 was merely tangential. Further, Amgen defends the district court's conclusion that Amgen successfully rebutted the *Festo* presumption under the "some other reason" rationale. Amgen argues that because a person of ordinary skill in the art would have understood the claims to encompass a 165-amino acid equivalent, the *Festo* presumption was rebutted. Finally, Amgen argues that the district court erred in finding that a 165-amino acid equivalent was foreseeable because the patentee expected the claims to encompass this equivalent.

C.

The burden of rebutting the *Festo* presumption lies with the patentee. *Festo III*, 344 F.3d at 1368. Whether a patent-holder has successfully rebutted the *Festo* presumption of the surrender of equivalents is a question of law, which we review de novo. *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1376 (Fed. Cir. 2005); *see also Festo III*, 344 F.3d at 1368; *Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1302 (Fed. Cir. 2005); *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1351 (Fed. Cir. 2004). For the reasons which follow, we uphold the district court's finding that Amgen failed to show that EPO with a 165-amino acid sequence was not foreseeable at the time of the amendment. However, we hold that the district court erred when it held that Amgen had met its burden of rebutting the *Festo* presumption under both the tangentiality and "some other reason" rationales.

The presumption that equivalents are surrendered may be rebutted if a patentee shows that "one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo III*, 344 F.3d 1365 (quoting *Festo II*, 535 U.S. at 741). As noted, in *Festo II*, the Supreme Court listed three ways in which a patentee may make this showing. First, the patentee may demonstrate that "the equivalent [would] have been unforeseeable at the time of the [amendment]." 535 U.S. at 740-41. Second, the patentee may show that "the rationale underlying the amendment [bears] no more than a tangential relation to the equivalent in question." *Id.* Third, a patentee may demonstrate that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Id.*

In *Festo III*, we offered some guidance as to what must be shown by a patentee in order to succeed in rebutting the *Festo* presumption under each of the three showings enumerated by the Supreme Court. In order to demonstrate that an invention

is not foreseeable, a patentee may utilize extrinsic evidence. 344 F.3d at 1369. We suggested that after-arising technology is more likely to be unforeseeable than old technology, but did not set forth any hard or fast rule on foreseeability. *Id.* We stated that "if the alleged equivalent were known in the prior art in the field of the invention, it certainly should have been foreseeable at the time of the amendment." *Id.* With regard to the tangentiality of an amendment to an equivalent, we did not set forth any concrete definition, but we did note that an amendment "made to avoid prior art that contains the equivalent in question is not tangential; it is central to allowance of the claim." *Id.* Thus, an amendment is tangential when the "reason for [it] was peripheral, or not directly relevant, to the alleged equivalent." *Id.* The determination of whether or not an amendment is merely tangential to the equivalent is based on the "patentee's objectively apparent reason for the narrowing amendment." *Id.* Thus, the inquiry must be based on the intrinsic record alone and, if necessary, expert testimony to aid in interpretation of that record. *Id.* Finally, we noted that the third way to rebut the *Festo* presumption, the "some other reason" route, is a narrow one. *Id.* at 1370. We stated that "the third criterion may be satisfied when there was some reason, such as the shortcomings of language, why the patentee was prevented from describing the alleged equivalent when it narrowed the claim." *Id.*

1.

With regard to the first *Festo* rebuttal argument, foreseeability, we see no error in the district court's holding that, at the time the third preliminary amendment was made, EPO with 165 amino acids was a foreseeable equivalent. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 147-49. We reject Amgen's assertion that the relevant inquiry is whether it was "objectively foreseeable that the amended claim language would not read on the accused equivalent." Appellee's Br. at 74. The question of how a person of

ordinary skill in the art would understand claims 2-4 of the '080 patent is one of claim construction, which was settled in *Amgen II*. 314 F.3d at 1344-45 (affirming the district court's construction of claims 2-4 as being limited to EPO with 166 amino acids). EPO with a 165-amino acid sequence was a foreseeable equivalent because the patentee admittedly knew about the 165-amino acid equivalent at the time of the third preliminary amendment. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157 (finding that during prosecution Amgen informed the examiner that human EPO has 165 amino acids); *see Festo III*, 344 F.3d at 1369 (noting that if an equivalent is known in the field, then it is foreseeable); *Glaxo Wellcome, Inc.*, 356 F.3d at 1355-56 (finding that a patentee did not rebut the presumption of surrender when a person of ordinary skill in the art at the time of the amendment would have considered the equivalent).

2.

We next examine whether Amgen has met its burden of showing that the reason for the addition of the reference to the "amino acid sequence of FIG. 6" was merely tangential to the alleged equivalent.

In *Insituform Technologies, Inc. v. CAT Contracting, Inc.*, 385 F.3d 1360 (Fed. Cir. 2004), we were asked to review whether a patentee had successfully rebutted the surrender of equivalents. *Id.* at 1370-71. The patented method in *Insituform* involved using a vacuum to impregnate a flexible tube with resin. *Id.* at 1362-63. During prosecution, the patentee limited the number of suction cups that could be placed on the tube to create the vacuum to just one cup. *Id.* at 1366. The amendment that limited the number of vacuum cups was made to overcome prior art which had a single vacuum source located at the end of the tube a distance from the resin source. *Id.* at 1370. The reason for the amendment was to clarify the location of the vacuum source relative to the resin—not to limit the number of vacuum cups. *Id.* Thus, we ruled that the

reason for the amendment was merely tangential to the alleged equivalent using multiple cups. *Id.* Accordingly, we held that the patentee in *Insituform* successfully rebutted the *Festo* presumption of surrender of the equivalent in question.

Amgen was required to show that the reason for adding the requirement in the third preliminary amendment that EPO have 166 amino acids was peripheral to the 165-amino acid equivalent. *See Festo III*, 344 F.3d at 1369. As seen, the third preliminary amendment was made to avoid a double patenting rejection in light of the '933 patent. *Amgen I*, 126 F. Supp. 2d at 135. Thus, the 165-amino acid equivalent is only tangential if the patentee's reason for limiting the '080 patent to EPO with 166 amino acids was unrelated to distinguishing the scope of the '080 patent from the scope of the '933 patent.

We must reject Amgen's argument that the sole reason for the amendment requiring EPO with 166 amino acids was to limit the '080 patent to *human* EPO and that therefore the amendment was merely tangential to a 165-amino acid equivalent. As seen, in claim 1 the '933 patent claimed:

> A non-naturally occurring erythropoietin glycoprotein product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

'933 patent, col. 38, ll. 18-22. Thus, claim 1 contains no limitation pertaining to human or non-human EPO. Claim 1 of the '933 patent, which covers both human and non-human EPO, also lacks any limitation concerning the amino acid sequence of the claimed EPO product. Accordingly, claim 1 of the '933 patent broadly encompasses EPO with any amino acid sequence, which would include amino acid sequences differing from that set forth in Figure 6.

We think Amgen's third preliminary amendment did more than limit the scope of the asserted claims of the '080 patent

to human EPO. The third preliminary amendment limited the '556 application, and consequently the '080 patent, to EPO having 166 amino acids. Claim 68, which was added with the second preliminary amendment to the '556 application, encompassed cells "encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof." Thus, after the second preliminary amendment, the '556 application and the '933 patent overlapped in claim scope. That is because the '556 application encompassed EPO having the incomplete amino acid sequence set forth in Figure 6. Likewise, claim 1 of the '933 patent encompassed EPO having any amino acid sequence, which would include an incomplete amino acid sequence of Figure 6. In other words, an incomplete amino acid sequence of Figure 6 (a "fragment") was encompassed by both the '556 application and the '933 patent. The deletion of "or fragment thereof" with the third preliminary amendment limited the '556 application to the complete 166-amino acid sequence shown in Figure 6. This limitation reduced the overlap between the scope of the '556 application, which encompassed only EPO with the complete amino acid sequence of Figure 6, from the scope of claim 1 of the '933 patent, which encompassed EPO with any amino acid sequence. Indeed, as the inventor himself stated in the remarks accompanying the third preliminary amendment, the amended claims "all differ in scope from glycoprotein claim 1 of [the '933 patent] in specifying that the claimed subject matter comprises the mature human erythropoietin *sequence of Figure 6*." Third Preliminary Amendment at 164 (Dec. 20, 1996), *quoted in Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 152 n.36 (emphasis added) (footnote omitted). Accordingly, the limitation added in the third preliminary amendment may have been central to overcoming a double patenting rejection in light of claim 1 of the '933 patent. Under these circumstances we cannot say that the reason for the addition of the limitation pertaining to the complete amino acid sequence of Figure 6 was merely tan-

gential to the alleged 165-amino acid equivalent. Thus, unlike *Insituform*, where it was clear that the amendment in question was not made to limit the number of cups and overcome the prior art, the requirement that EPO have exactly 166 amino acids may have been central to the allowance of claims 2-4 over a double patenting rejection.

Finally, we think that if the patentee had wished only to limit the claims to human EPO, the patentee could have done so by continuing to use the adjective "human" when referring to EPO in the third preliminary amendment; instead the patentee chose to further narrow the claims in the third preliminary amendment by making reference to the specific sequence in Figure 6 rather than human EPO. We thus hold that Amgen has not met its burden of showing that the addition of the "the mature amino acid sequence of FIG. 6" amendment was tangential to a 165-amino acid equivalent.

3.

In the alternative, the district court relied on the "some other reason" language in the Supreme Court's *Festo II* decision in ruling that Amgen had rebutted the *Festo* presumption of surrender of equivalents. In *Festo II*, the Court held that the presumption of the surrender of equivalents could be rebutted by showing that "there [is] some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." 535 U.S. at 740-41. As previously noted, the district court based its conclusion that Amgen had rebutted the *Festo* presumption under the "some other reason" rationale on its finding that, before the patentee made the third preliminary amendment, the patentee disclosed information to the Patent and Trademark Office concerning the fact that human EPO has 165 amino acids. *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157. The district court also relied on extrinsic evidence that a person of ordinary skill in the art would understand that Amgen meant to claim human EPO

having either 165 or 166 amino acids at the time the third preliminary amendment was made. *Id.* The court reasoned that Amgen had rebutted the *Festo* presumption under the "some other reason" criterion because the patentee could not have reasonably been expected to have described the 165-amino acid equivalent because those of skill in the art would have interpreted the amendment to cover the 165-amino acid equivalent. *Id.* at 158.

However, the district court's analysis does not correctly apply the Supreme Court's explanation of the "some other reason" rebuttal argument: the other reason must be such that the patentee could "not reasonably be expected" to write a claim to encompass the equivalent, *see Festo II*, 535 U.S. at 741, such as a shortcoming of language, *Festo III*, 344 F.3d at 1370. The patentee knew of the 165-amino acid sequence at the time of the amendment, *Amgen III Doctrine of Equivalents Judgment*, 287 F. Supp. 2d at 157, but chose to limit the claims to the 166-amino acid sequence depicted in Figure 6. Contrary to Amgen's argument, whether the patentee, the examiner, or a person of skill in the art may have thought the claims encompassed EPO with 165 amino acids does not excuse the patentee's failure to claim the equivalent. *See Biagro*, 423 F.3d at 1307 (rejecting the patentee's argument that the "some other reason" rebuttal argument applied when the patentee allegedly understood the claim language to refer to the equivalent in question). Further, there were no shortcomings of language that might have prevented the patentee from claiming EPO having 165 amino acids. The patentee could have simply claimed mature human EPO without reference to Figure 6. Alternatively, the patentee could have claimed, as it did prior to the third preliminary amendment, EPO having the amino acid sequence disclosed in Figure 6 or a "fragment thereof." In short, there was no linguistic barrier to claiming EPO comprised of 165 amino acids. Amgen has not argued on appeal, nor do we find, that any other reason exists that might rebut the *Festo* presumption. Therefore, we

find that the patentee could have reasonably been expected to accurately point out and particularly claim the 165-amino acid sequence.

The facts in this case are analogous to those in *Festo III*, where we ruled that the *Festo* presumption was not rebutted by "some other reason." In *Festo III*, we rejected Festo's argument that it was not estopped from asserting the doctrine of equivalents because the patentee "could not reasonably have been expected to have drafted a claim to cover what was thought to be an inferior and unacceptable design." 344 F.3d at 1372-73. Like the patentee in *Festo*, who knew about the "inferior" equivalent, the patentee of the '080 patent knew about the 165-amino acid sequence at the time of the amendment, but still chose to claim the incorrect 166-amino acid sequence in Figure 6. We conclude that Amgen has not rebutted the *Festo* presumption based on "some other reason."

In sum, we uphold the district court's finding that the 165-amino acid EPO equivalent was foreseeable at the time of the third preliminary amendment. The district court erred, however, in finding that Amgen successfully rebutted the *Festo* presumption of surrender of equivalents under both the tangentially related rebuttal argument and the "some other reason" rebuttal argument. This means that HMR/TKT cannot be found to have infringed the claims 2-4 of the '080 patent under the doctrine of equivalents. Accordingly, the judgment of infringement of claims 2-4 is reversed. It is unnecessary for us to reach HMR/TKT's alternative argument by way of affirmative defense that claims 2-4 of the '080 patent are invalid as anticipated by the Goldwasser reference.

III.

The '698 and '349 patents

The '698 patent is directed to a process for producing EPO in host cells using recombinant DNA techniques. On remand, in *Amgen III Validity & Literal Infringement Judgment*, the

district court rejected HMR/TKT's argument that the asserted claims of the '698 patent (claims 4-9) are invalid because they lack an adequate written description. The court also rejected HMR/TKT's argument that the asserted claims were not enabled. Having rejected HMR/TKT's validity challenges, the court found claims 4-9 of the '698 patent literally infringed.

The '349 patent is directed to vertebrate cells capable of producing EPO and a process for making EPO using the claimed cells. On remand, the district court rejected HMR/TKT's argument that the asserted claims of the '349 patent (claims 1, 3, 4, 6, and 7) were invalid by reason of obviousness. Since the district court already had ruled in *Amgen I* that claims 1, 3, 4, and 6 of the '349 patent were infringed, in *Amgen III Validity & Literal Infringement Judgment* it only was necessary for the court to address Amgen's claim that HMR/TKT's HMR4396 literally infringed claim 7 of the '349 patent. Doing so, the court found literal infringement. 339 F. Supp. 2d at 258, 336.

On appeal, HMR/TKT argues that the district court made various claim construction errors and also erred in its validity and infringement rulings in the case of both the '698 and '349 patents. We have carefully considered all of HMR/TKT's arguments relating to the '698 and '349 patents. Having done so, we see no error in the district court's legal conclusions; nor do we see clear error in its findings of fact. Accordingly, we affirm in all respects the court's rulings with respect to the '698 and '349 patents.

CONCLUSION

For the foregoing reasons, we vacate the district court's judgment that claim 1 of the '422 patent is not invalid under 35 U.S.C. § 102(a) and remand to the district court for a determination of whether, in view of our construction of the limitation "therapeutically effective," claim 1 is anticipated

by the Goldwasser reference and for such further proceedings as may be necessary.[11] We reverse the court's judgment that HMR/TKT infringes claims 2-4 of the '080 patent under the doctrine of equivalents. We affirm the court's judgment that HMR/TKT infringes claims 4-9 of the '698 patent and claims 1, 3, 4, 6, and 7 of the '349 patent.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART, and REMANDED

[11] See footnote 10, *supra*.

MICHEL, *Chief Judge*, dissenting-in-part.

I write separately to voice my strong disagreement with the majority's holdings that (1) contrary to the district court's construction, "therapeutically effective" in claim 1 of the '422 patent means simply eliciting in vivo biological effects even if not tending to cure certain diseases and (2) claim 1 of the '422 patent could therefore be invalid in light of the Goldwasser reference, which describes a prior art compound eliciting biological activity without curing. Because the majority concludes that the district court erred in construing "therapeutically effective" to mean having a disease-curing effect, it remands the case for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of this particular patent, only one of several asserted.

At the outset, I compliment the district court for the meticulous attention it has given to this extraordinarily complicated, highly-technical, and very difficult case. The district court's two opinions on remand, the subject of our present review, were well-reasoned, well-grounded in the evidence, and well-written. The trial court clearly exerted tremendous effort to carefully consider all the issues raised by the parties as well as our remand instructions in *Amgen II*.

After discovery, the district court conducted a three-day Markman hearing and a bench trial spanning twenty-three days in 2000 and then, following our remand, a second *Markman* hearing and second bench trial spanning nine days in 2003. The district court also took the creative steps of employing Professor Chris Kaiser of the Massachusetts Institute of Technology as a technical advisor on the underlying technology and Michele D. Beardslee as a special master to aid in researching the law, analyzing the issues, and drafting the remand opinion. Assisted by them, the district court spent more than ten months rendering its revised claim constructions and making extensive findings of fact and conclusions of law; it subsequently issued two opinions, together totaling

over 360 pages. Plainly, these decisions were not reached in a haphazard or hurried manner by a court intimidated by either the science or the law. On the contrary, the district court's management and resolution of this case is, I think, a model for all trial courts confronted with such patent suits.

I.

The district court construed "therapeutically effective amount" to mean "a quantity that produces a result that in and of itself helps to heal or cure." *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 245. It further elaborated that a therapeutically effective amount would elicit certain in vivo biological effects, such as those described in the specification, col. 33, ll. 17-22, (i.e., stimulation of reticulocyte response, development of ferrokinetic effects, erythrocyte mass changes, stimulation of hemoglobin C synthesis, and increasing hematocrit levels), which reflect a "healing" or "curing" effect in "patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiological anemias, and the like." '422 patent, col. 33, ll. 23-28. I believe the court correctly recognized that merely eliciting a biological effect is not the same as being therapeutically effective.

Indeed, prior art compounds could trigger the very in vivo biological effects enumerated in the specification but were utterly incapable of "healing" or "curing" the class of patients described in the '422 patent. Notably, an article published in the Renal Extrarenal Sources of Erythropoietin Journal in 1971 revealed that a patient suffering from renal anemia was treated with an urinary EPO preparation but, despite experiencing an increase in reticulocytes, died five days later. The district court was particularly aware of this article and even mentioned it when addressing the issue of obviousness after

the first bench trial. *See Amgen I*, 126 F. Supp. 2d at 116. Had this uEPO or any other prior art EPO product been shown to "heal" or "cure" anemia or similar blood disorders, there would have been little need for the claimed invention.

When a compound is truly "therapeutically effective," that is, when it "heals" or "cures" such a blood disorder, it necessarily increases hematocrit as well as causes one or more of the other listed in vivo biological effects. Reading lines 17-22 of column 33 in context, the patentee clearly recognized this.

> As previously indicated, recombinant-produced and synthetic products of the invention share, to varying degrees, the in vitro biological activity of EPO isolates from natural sources and consequently are projected to have utility as substitutes for EPO isolates in culture media employed for growth of erythropoietin cells in culture. Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., . . . *and*, as indicated in Example 10, *increasing hematocrit levels* in mammals.

'422 patent, col. 33, ll. 6-22 (emphasis added). This disclosure clarifies three aspects of the claimed invention. First, the claimed EPO shares the in vitro biological activity of natural EPO. Second, the claimed EPO elicits the very same in vivo activity as natural EPO and, therefore, is suitable for use in EPO therapy procedures. Third, the claimed EPO increases hematocrit in mammals, as exemplified in Example 10 of the '422 patent. By reciting "therapeutically effective amount of human erythropoietin," the patentee thus demonstrated an intention to claim EPO that (1) causes the same in vivo biological effects as the natural EPO; and also (2) increases hematocrit.

The subsequent disclosure strengthens my view that the district court correctly construed the "therapeutically effective" limitation.

> A preferred method for administration of polypeptide products of the invention is by parenteral (e.g., IV, IM, SC, or IP) routes and the compositions administered would ordinarily include *therapeutically effective* amounts of product in combination with acceptable diluents, carriers and/or adjuvants. . . . Effective dosages are expected to vary substantially depending upon the condition treated but therapeutic doses are presently expected to be in the range of 0.1 (~70) to 100 (~7000 U) μg/kg body weight of the active material.

'422 patent, col. 33, ll. 41-52 (emphasis added). In the only part of the specification where the term "therapeutically effective" actually appears, the patentee uses the term in the ordinary sense of the phrase to mean promoting "healing" or "curing." That is, the patentee teaches the preferred amount of EPO product and a preferred method of administration for a patient suffering from a disorder characterized by a low red blood cell count. Inherently, the ultimate goal is to "heal" or "cure" the disorder. That healing is characterized by an increased red blood cell count, i.e., a higher hematocrit level.

Significantly, I note that the words "therapeutically effective" are conventionally employed in the pharmaceutical arts to indicate that the claimed pharmaceutical product has utility in the treatment of a human disease where such treatment tends to cause the "healing" or "curing" of the disease. The patentee, I think, intended to invoke that very convention. While the majority might be correct that the '422 patent is not necessarily limited to the exact class of patients described in the specification (as opposed to other blood disorders associated with low hematocrit levels), the district court correctly recognized that it would be "foolish to construe a term such as 'therapeutically effective,' without reference to a

class of patients for which the product is intended to be 'therapeutically effective.'" *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 237.

The specification further discloses various analogs of EPO at columns 35-36:

> In addition to naturally-occurring allelic forms of mature EPO, the present invention also embraces other "EPO products" such as polypeptide analogs of EPO and fragments of "mature" EPO. . . . Especially significant in this regard are those potential fragments of EPO which are elucidated upon consideration of the human genomic DNA sequence of FIG. 6, i.e., "fragment" of the total continuous EPO sequence which are delineated by intron sequences and which may constitute distinct "domains" of biological activity. It is *noteworthy that the absence of in vivo activity for any one or more of the "EPO products" of the invention is not wholly preclusive of therapeutic utility (see, Weiland, et. al., supra) or of utility in other contexts, such as in EPO assays or EPO antagonism.*

'422 patent, col. 35, ll. 34-37; col. 36, ll. 4-14. The majority mistakenly relies on this disclosure to support its view that the "therapeutically effective" means merely capable of triggering *any* in vivo biological activity, regardless of degree. Correctly read, the emphasized passage plainly concerns only analogs of EPO, not the EPO of claim 1. That is, the full disclosure teaches that *analogs* of EPO may offer therapeutic utility even though they may not have in vivo activity. The emphasized sentence says nothing about the *claimed* EPO and hence cannot be relied upon to construe the "therapeutically effective" limitation.

The prosecution history further confirms that "therapeutically effective" connotes more than simply eliciting any cited in vivo biological effect. The district court emphasized that

during prosecution of the '422 patent, the patentee differentiated its invention from natural EPO, which also elicits the aforementioned biological activity, on the basis that the latter was not available in large enough quantities to treat patients, i.e., help cure their diseases. *Amgen III Validity & Literal Infringement Judgment*, 339 F. Supp. 2d at 239. Likewise, during the prosecution of the Application No. 07/113,178, a parent application of the '422 patent which itself issued as United States Patent No. 5,441,868, the patentee distinguished the claimed EPO from the prior art, emphasizing that the claimed EPO could be used as a therapeutic product to treat humans with blood disorders characterized by a low red blood cell count whereas the prior art EPO could not. In particular, the patentee stated:

> [N]aturally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proved to be clinically effective, and is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

In so differentiating the claimed EPO from the prior art, the patentee said that the claimed EPO is capable of doing more, i.e., the claimed EPO "heals" or "cures" anemia and other such disorders by raising a patient's red blood cell count.

Thereafter, during the prosecution of the Application No. 08/100,197, a continuation of Application No. 07/113,178 discussed above, the examiner objected that "Claim 62 is vague and indefinite because it is unclear what the claimed composition is required to be 'effective' for." In response, after quoting column 33, lines 11-28, which includes a description of the in vivo biological effects, the "increasing hematocrit" language, and various diseases treatable with the claimed invention, the patentee again explained that the

claimed EPO could be used to treat, (i.e., "heal" or "cure"), various blood disorders:

> It is believed that these sentences from the specification and others provide a clear and definite description of the uses for which the claimed erythropoietin compositions would be therapeutically effective. A person of skill in the art would understand that the amount of erythropoietin necessary to achieve these *defined therapeutic results* would vary for each use. However, clinicians can readily determine the "therapeutically effective" amounts for each condition, and indeed for each patient. Application submits that the claim language "therapeutically effective amount" is commonly used in this type of case where the product is usable to treat various conditions.

(emphasis added). Accordingly, I must conclude that the district court's construction of the "therapeutically effective" limitation comports with the patentee's own repeated descriptions of the claimed invention. It is exactly the way a skilled artisan would interpret the patent, as the district court held.

II.

Regarding possible anticipation of the invention of the '422 patent by the Goldwasser reference, the district court set forth very specific reasons why none of the in vivo biological effects mentioned in the Goldwasser reference (i.e., an increase reticulocytes, an increase in plasma iron clearance, and red cell mass changes) demonstrated therapeutic effectiveness. HMR does not contend that the district court clearly erred. Rather, it merely asserts that all of these biological results fall under its proposed claim construction for the term "therapeutically effective amount," which is any amount of EPO that elicits any in vivo biological effect, even if not accompanied by an increased hematocrit. Because I think that the district court correctly rejected HMR's proposed construction and properly construed "therapeutically effective" to

mean "healing" or "curing," HMR's validity challenge necessarily fails. While all of the results described in the Goldwasser reference represent in vivo biological responses, none demonstrate that the subject anemic patients were even partially "healed" or "cured." In fact, Dr. Goldwasser himself considered his study a failure because the patients' hematocrit levels did not increase. I therefore conclude that the district court correctly found that the Goldwasser reference does not anticipate claim 1 of the '422 patent. Clear error has not been shown. We should therefore affirm the judgment as to validity.

III.

This litigation has already dragged on for almost ten years, yet the end is nowhere in sight. The majority again remands this case to the district court, this time for a re-adjudication of whether the Goldwasser reference anticipates claim 1 of the '422 patent in light of its revised construction of "therapeutically effective." The district court, as a result, will conduct further proceedings and render a third opinion. Inevitably, at least one party will appeal that judgment, prompting a third review by this Court. We, in turn, will issue another opinion, perhaps even remanding the case a third time. The district court, however, has yet to decide whether to grant an injunction, the specific relief sought by the patentee. Presumably, after our decision in that potential third appeal, the district court would conduct a trial or hearing on that issue and reach another decision, which will likely be appealed by one or both of the parties. We consequently would hear a fourth appeal and issue a fourth decision, which could involve yet another remand. When will it end? Ironically, the patents in dispute may expire before this litigation concludes.

Moreover, since the majority holds that other asserted patents are not invalid and are literally infringed by HMR 4396, (and here I agree), the district court likely will enter an injunction precluding appellants from marketing HMR 4396

until the expiration of at least the '698 and '349 patents. Prolonging this litigation seems futile when, in the end, an injunction will likely issue regardless of how "therapeutically effective" is construed or whether claim 1 of the '422 patent is invalid.

APPENDIX B

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

MEMORANDUM AND ORDER

YOUNG, C.J. October 15, 2004

I. INTRODUCTION

This patent infringement action concerns patents held by Amgen, Inc. ("Amgen"), relating to the manufacture of a recombinant (genetically engineered) DNA[1] product, known as epoietin alfa,[2] that is similar to natural erythropoietin ("EPO"), a hormone that stimulates production of red blood cells, and is useful in, among other things, treating patients who need of blood transfusions and suffer from blood composition disorders such as hemophilia, anemia, and sickle cell disease. This product and this case are not new to the public or to this Court. The case began brewing in 1997, when Amgen filed a declaratory judgment in the United States District Court for the District of Massachusetts against

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[1] "DNA" is short for "deoxyribonucleic acid."

[2] This product is sold under the trademark EPOGEN®.

Defendants Hoechst Marion Roussel, Inc.[3] and Transkaryotic Therapies, Inc. (collectively "HMR/TKT") claiming that three of its patents were infringed by HMR/TKT's human EPO product, "HMR 4396," produced from the R223 cell line grown in culture. *See Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 106 (D. Mass. 1998). In 1999, Amgen amended the complaint to include two other patents. *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 96-98 (D. Mass. 2001) ("*Amgen I*"). A lengthy jury-waived trial ensued. It commenced in May 2000 and lasted twenty-three days over the course of four months. *Id.* at 78. Not surprisingly, HMR/TKT appealed this Court's decision, *Amgen I*, 126 F. Supp. 2d 69. In *Amgen Inc.* v. *Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003) ("*Amgen II*"), the Federal Circuit affirmed a majority of this Court's findings and rulings but vacated and remanded a few issues to this Court. *Id.* at 1358. This memorandum and order addresses those issues on remand, some of which have already been decided by the Court and announced to the parties, thus requiring only a brief review.

II. BACKGROUND: PROCEDURAL AND SUBSTANTIVE HISTORY

A. The Patents at Issue

There were originally five patents at issue in this case. Only four, however, remain on remand. The patents and claims now at issue are: Claim 1 of U.S. Patent No. 5,955,422 (issued Sept. 21, 1999) ("'422 patent"); Claims 2-4 of U.S. Patent No. 5,621,080 (issued Apr. 15, 1997) ("'080 patent"); Claims 4-9 of U.S. Patent No. 5,618,698 (issued Apr. 8, 1997) ("'698 patent"); and Claims 1, 3, 4, 6, and 7 of U.S.

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[3] Hoechst Marion Roussel, Inc. is now known as Aventis Pharmaceuticals, Inc.

Patent No. 5,756,349 (issued May 26, 1998) ("'349 patent"). *Amgen I*, 126 F. Supp. 2d at 79; *Amgen II*, 314 F.3d at 1320.[4]

Although the patents vary, they all share a common disclosure and identical specifications. *Amgen I*, 126 F. Supp. 2d at 79. For ease of reference, the Court cites to the specification found in the '933 patent, which is identical to the specification of the patents in dispute on remand. '933 Patent, Ex. 1.[5]

B. The Technology

As *Amgen I* set out the basics of the underlying technology in detail, only a brief summary is provided here. EPO is a naturally occurring hormone that controls erythropoiesis, the production of red blood cells in bone marrow. '933 Patent, Ex. 1, col. 5: 39-67. Erythropoiesis occurs continuously to offset cell destruction. *Id.* It enables a sufficient (but not excessive) amount of red blood cells to be available in the blood to provide tissue oxygenation. *Id.* Hemoglobin is the protein in the red blood cells that actually transports the oxygen. *Amgen I*, 126 F. Supp. 2d at 98. The amount of hemoglobin correlates to the amount of oxygen. *Id.* Hematocrit, which indicates the relative proportion of red blood cells to the total volume of blood, measures the ability of the blood to supply oxygen to the body. *Id.* Thus, generally an increase or

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[4] The fifth patent involved in *Amgen* I was U.S. Patent No. 5,547,933 (issued Aug. 20, 1996) ("'933 patent"). Since this Court's ruling that the '933 patent was invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2 was upheld on appeal, *Amgen II*, 314 F.3d at 1342, that patent will not be addressed in this memorandum and order.

[5] Because many of the exhibits from the first trial were used in the second trial and the numbering system was simply continued in the second trial, the Court will not designate from which trial the exhibits came but instead simply refer to the trial exhibit number. When citing testimony, however, the Court will refer to the second trial as the "remand trial" and cite it as "R. Trial," while the first trial will simply be cited as "Trial."

decrease in hematocrit equates with an increase or decrease in the ability to supply oxygen to the body. *Id.* Under normal conditions, a person has a hematocrit of about forty-five to fifty, which means forty-five to fifty percent of the blood is made up of red blood cells. *Id.*

EPO is produced in the kidney and liver. Therefore, patients with chronic renal failure lack normal levels of EPO and suffer from anemia. *Amgen II*, 314 F.3d at 1321. Introduction of additional EPO into the patient's body can increase a patient's hematocrit level and sustain it at or near normal levels. *Id.* In other words, the blood is able to provide a steady supply of sufficient oxygen to the tissues. *Id.*; *Amgen I*, 126 F. Supp. 2d at 99.

Early attempts to obtain EPO from plasma or urine proved unsuccessful because the body only produces human EPO in very small amounts, '933 Patent, Ex. 1, col. 5: 54-58, and the techniques were very complicated and resulted in the collection of very small amounts of impure and unstable amounts of EPO, *id.* at col. 6: 60-65. Amgen is recognized as the pioneer in the production of a therapeutically effective amount of EPO via recombinant EPO ("rEPO") techniques. *See, e.g., Molecular Biology and Biotechnology: A Comprehensive Desk Reference* 108 (Robert A. Meyers ed., VCH Publishers 1995).

Dr. Fu-Kuen Lin ("Lin"), the named inventor of all the patents in issue, isolated and characterized DNA sequences encoding EPO from humans and monkeys. '933 Patent, Ex. 1, col. 13: 50-53. Lin determined the DNA sequence of human EPO and its predicted amino acid sequence. '933 Patent, Ex. 1, col. 10: 65-11: 2. Lin then produced large amounts of EPO by using recombinant DNA technology. *Id.* at col. 14: 23-29. In the patent specification, many methods of producing EPO are described. EPOGEN® is produced by the method described in Example 10, wherein human EPO is produced by introducing exogenous DNA into host Chinese hamster ovary

("CHO") cells. *Id.* at col. 25: 30-29: 7.[6] The rEPO that is produced has the same or similar amino acid sequences or primary structural conformation as that of naturally-occurring EPO. *Id.* at col. 29: 1-7. As a result, it possesses one or more the biological properties of naturally-occurring EPO but differs from natural EPO in its "glycosylation," that is, it has a different average carbohydrate composition. *Id.* at col. 10: 35-41.

HMR/TKT, in producing its human erythropoietin, HMR 4396 (also called Gene-Activated EPO "GA-EPO"), also uses recombinant technology. HMR/TKT, however, does not use a host cell from a non-human species but manipulates the ordinarily unexpressed human EPO gene where it naturally resides. *Amgen I*, 126 F. Supp. 2d at 102. In that way, the human EPO DNA material is endogenous to the human cell. *Id.* After introducing a promoter sequence, human EPO is expressed in a human rather than a hamster cell. *Id.*

C. The Federal Circuit's Decision

A brief review of the key rulings and findings that were affirmed and remanded on appeal follows:

1. Claim Construction

a. Affirmed

The Federal Circuit upheld all of the Court's claim constructions. *Amgen II*, 314 F.3d at 1320. Specifically, the Federal Circuit upheld this Court's construction that Amgen's claims do not limit the invention to using only exogenous

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[6] Amgen transfects CHO cells with a vector that contains both viral promoter DNA and the human EPO gene. '933 Patent, Ex. 1, col. 25: 58-61; *Amgen I*, 126 F. Supp. 2d at 102. Therefore, the human EPO DNA material is exogenous to the hamster host cell because it was removed from the cell in which it originated, placed in a vector, and reintroduced into a host cell. *Amgen I*, 126 F. Supp. 2d at 102. This is called heterologous recombination. *Id.*

DNA (as opposed to endogenous DNA). *Id.* at 1327. It also upheld this Court's determinations that (1) non-naturally occurring means "'not occurring in nature'"; (2) vertebrates are anything with "'a segmented bony or cartilaginous spinal cord' which obviously includes humans"; and (3) humans are a subset of mammals and mammals are a subset of vertebrates. *Id.* at 1327-28 (quoting *Amgen I*, 126 F. Supp. 2d at 85, 90-91). To that end, the Federal Circuit agreed that the specification indicates that the invention uses human DNA in human host cells in culture. *Id.*

The Federal Circuit also upheld the Court's determination that claim 1 of the '422 patent, claims 2, 3, and 4 of the '080 patent, and claims 1, 3, 4, and 6 of the '349 patent are product claims (not process claims) and thus are not restricted or defined by any method of production or any particular source, other than what is specifically excluded. *Amgen II*, 314 F.3d at 1329-30.

b. Remanded

Although all the terms that this Court construed in *Amgen I* under the principles of *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), were upheld, the Federal Circuit remanded to this Court the construction of the term "therapeutically effective."[7] *Amgen II*, 314 F.3d at 1354. This phrase was not considered by the Court to be in dispute during the first trial. In its written analysis, however, this Court interpreted the term. *Amgen I*, 126 F. Supp. 2d at 112; *see also id.* at 99. While interpreting a term to provide context for the discussion is proper when the term is not in dispute, the Federal Circuit determined that the term "therapeutically effective" actually was in dispute "because it is central to whether Goldwasser is properly considered prior art." *Amgen II*, 314 F.3d at 1353. Therefore, it remanded so this Court could construe "thera-

[7] The term "therapeutically effective" is found in claim 1 of the '422 patent and in claim 4 of the '080 patent.

peutically effective" pursuant to *Markman*. *Id.* at 1358. Since claim construction is matter of law, *Markman*, 517 U.S. at 386; *but see* Arthur R. Miller, *The Pretrial Rush to Judgment: Are the "Litigation Explosion," "Liability Crisis," and Efficiency Clichés Eroding Our Day in Court and Jury Trial Commitments?*, 78 N.Y.U. L. Rev. 982, 1087 (2003) (criticizing the decision in *Markman*), the Federal Circuit could have proceeded to construe the phrase itself. Where a word or phrase has not been first construed in the district court, the Federal Circuit follows the courteous and prudential path of first seeking claim construction below. Hon. Pauline Newman, Remarks at the American Law Inst.-Am. Bar Assoc. Panel on the Trial of a Patent Case (Sept. 18, 2003).

2. Infringement

a. Affirmed

The Federal Circuit affirmed this Court's ruling on summary judgment that claim 1 of the '422 patent is literally infringed. *Amgen II*, 314 F.3d at 1348. It also affirmed this Court's ruling that the '080 patent is not literally infringed by HMR/TKT's HMR 4396, *id.* at 1344-45, but that claims 1, 3, 4, and 6 of the '349 patent are literally infringed by it, *id.* at 1351-52.

b. Remanded

(1) The '080 Patent

After finding that HMR 4396 did not literally infringe claims 2, 3, and 4 of the '080 patent because HMR 4396 comprised only 165 amino acids, *Amgen I*, 126 F. Supp. 2d at 99-101, this Court held that HMR 4396 performed substantially the same function in substantially the same way to obtain substantially the same result as the EPO glycoprotein of claims 2 and 3 of the '080 patent, *id.* at 133. Therefore, it ruled that Amgen's '080 patent was infringed by HMR/TKT's product under the doctrine of equivalents. *Id.*

In response to HMR/TKT's argument that Amgen should be estopped from arguing equivalent infringement, this Court ruled that prosecution history estoppel did not apply because Amgen did not add the "mature amino acid sequence of Figure 6" limitation "in an attempt to overcome a rejection [or] to avoid prior art," but, instead, to "demonstrate that 'same invention' type double patenting did not apply,"—that is, to distinguish the '080 patent from the '933 patent. *Id.* at 134-35.

The Federal Circuit agreed that the amendment was made for this purpose but made clear that under *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 731 (2002) ("*Festo II*"), "'a narrowing amendment to satisfy *any* requirement of the Patent Act may give rise to an estoppel.'" *Amgen II*, 314 F. 3d at 1345 (quoting *Festo II*, 535 U.S. at 736) (emphasis added). Therefore, it held that the presumption of prosecution history estoppel applied. *Id.* at 1345. The Federal Circuit then vacated this Court's finding of equivalent infringement and remanded for an analysis based on the "narrow ways of rebutting the Supreme Court's presumption of estoppel" outlined in *Festo II*. *Id.* at 1345.

(2) The '698 Patent

On appeal, the Federal Circuit vacated and remanded this Court's ruling regarding infringement of the '698 patent because this Court had compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347. Therefore, it remanded to this Court the question whether claims 4-9 of the '698 patent are infringed. *Id.*

(3) The '349 patent

Although this Court found that claims 1, 3, 4, and 6 of the '349 patent are literally infringed by HMR/TKT's 4396, it held that HMR/TKT did not literally or equivalently infringe claim 7, the process claim, of the '349 patent. *Amgen I*, 126

F. Supp. 2d at 122. The Court compared the accused process to the preferred embodiment in the claim and concluded that HMR/TKT's "process for producing erythropoietin differs markedly from that disclosed by Amgen's specification." *Id.* The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this ruling and remanded so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1350-51.

3. Inequitable Conduct

The Court's determination that HMR/TKT had not proven by clear and convincing evidence that the '933, '080, '349 and '422 patents were unenforceable due to inequitable conduct was affirmed on appeal. *Amgen II*, 314 F.3d at 1357-58.

4. Written Description, Definiteness, and Enablement

a. Affirmed

The Federal Circuit affirmed this Court's rulings that the '422, '080, and '349 patents are adequately described and enabled. *Id.* at 1337. In so ruling, the Federal Circuit explained that this Court "carefully considered these issues, finding in the end that HMR/TKT had not met its clear and convincing burden of proof." *Id.* Because the Federal Circuit found "no clear error in these factual determinations," and the parties did not allege any legal error, it reasoned that it would "not disturb [this Court's] holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1." *Id.*

As mentioned in an earlier footnote, *see* note 3, *supra*, this Court held and the Federal Circuit affirmed that the '933 patent (specifically the claims requiring "glycosylation which differs") was invalid for indefiniteness under section 112. *Amgen I*, 126 F. Supp. at 156-57. Therefore, the '933 patent is not at issue on remand.

5. Anticipation and Obviousness

a. Affirmed

The Court's ruling that the asserted claims of the '080, '349, and '933 patents are not anticipated under 35 U.S.C. § 102 by the Sugimoto reference was affirmed by the Federal Circuit. *Id.* at 1320, 1356.[8] In affirming, however, the Federal Circuit made clear that the Court's determination that Sugimoto was not enabled was an error, though harmless, because the Court put the burden of proving enablement of Sugimoto on HMR/TKT when the burden of proving non-enablement should have been put on Amgen. *Id.* at 1356.[9]

b. Remanded

The Federal Circuit remanded, however, the Court's findings that Sugimoto does not anticipate claim 1 of the '422 patent stating that the "district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of 'therapeutically effective'" and be "mindful of the principle that source limitations cannot impart novelty to old compositions." *Id.* at 1356.[10] Addi-

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[8] In its opinion, the Federal Circuit affirmed this Court's finding that Sugimoto did not anticipate the '080, '933, '349, and '698 patents. *Amgen II*, 314 F.3d at 1320, 1356. This Court, however, never addressed the validity of the '698 patent. It concluded that the '698 patent was not infringed literally or equivalently at the close of Amgen's direct case. *Amgen I*, 126 F. Supp. 2d at 101. Therefore, whether Sugimoto anticipates the '698 patent is one of the issues addressed in this memorandum and order.

[9] The error was harmless because the Court, despite having concluded that Sugimoto was not enabled, "nevertheless conducted a full anticipation analysis" and found that "'none of the cited references disclose[s] each and every limitation of any of Amgen's individual claims'" of the '080, '933 and '349 patents. *Amgen II*, 314 F.3d at 1356 (quoting *Amgen I*, 126 F. Supp. 2d at 109).

[10] It is clear from *Amgen II* that Amgen may on remand argue that the '422 patent is not anticipated because Sugimoto is not enabled. *See*

tionally, the Federal Circuit remanded this Court's finding that the '422, '080, and '349 patents were not obvious in light of Sugimoto because this Court based its decision, in part, on the fact that it concluded that Sugimoto was not enabled. *Id.* at 1357. The Federal Circuit explained that under section 103, a reference need not be enabled to qualify as prior art. *Id.*

In *Amgen I*, this Court found that the asserted claims of the '080, '422 and '349 patents were not anticipated or rendered obvious by the Goldwasser reference. *Amgen I*, 126 F. Supp. 2d 112-17. The Federal Circuit remanded these findings for further proceedings given that "therapeutically effective" was not construed in accordance with *Markman*. *Amgen II*, 314 F.3d at 1354. As mentioned above, it directed the Court to construe the term and determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. § 102(a) or § 103 in light of the Court's construction. *Id.* at 1354.

D. Procedural and Substantive History Since *Amgen II*

The Federal Circuit's decision issued on January 6, 2003. This Court received the action on remand on March 13, 2003 [Doc. No. 653], and it held a status conference on April 16, 2003 [Doc. No. 657]. On May 16, 2003, Amgen moved for: (1) judgment under Federal Rule of Civil Procedure 52(c) that claims 2-4 of the '080 patent were infringed under the doctrine of equivalents [Doc. No. 659]; (2) summary judgment of infringement of claims 4-9 of the '698 patent [Doc. No. 663]; (3) judgment pursuant to Rule 52(c) that claim 1 of the '422 patent and claim 4 of the '080 patent are valid [Doc. No. 670]; and (4) judgment pursuant to Rule 52(c) that claims 1, 3, 4, 6, and 7 of the '349 patent are valid and that claim 7

Amgen II, 314 F.3d at 1354-57. The burden of proving Sugimoto's non-enablement, however, rests with Amgen. Moreover, Amgen must present more evidence than that adduced in the first trial as the Federal Circuit made clear that the evidence from the first trial was insufficient to prove non-enablement.

of the '349 patent is infringed [Doc. No. 674]. HMR/TKT simultaneously moved for: (1) judgment that Amgen is estopped from asserting infringement of the '080 patent pursuant to the doctrine of equivalents [Doc. No. 678]; (2) judgment that claim 1 of the '422 patent is invalid as anticipated [Doc. No. 682]; (3) judgment pursuant to Rule 52(c) that the asserted process claims of the '698 patent and '349 patents are not infringed [Doc. No. 686]; and (4) judgment that the '422, '080, and '349 claims are invalid for obviousness [Doc. No. 690].

The memoranda in support of and in opposition to these motions raised additional issues that are reviewed in this opinion. They are described briefly below.

In its opposition to Amgen's renewed motion for summary judgment of infringement of the '698 patent,[11] HMR/TKT argued, among other things, that Amgen's proposed construction of the words "DNA encoding" found in claims 4 and 6 of the '698 patent is incorrect. HMR/TKT's Mem. in Opp'n re '698 [Doc. No. 700] at 7-8. Second, HMR/TKT argued that in claims 4 and 6 of the '698 patent, Amgen set forth a step-plus-function claim in referring to the "steps of . . . growing, under suitable nutrient conditions" and that an assessment of whether HMR/TKT infringed this aspect of the claim must focus on a comparison between HMR/TKT's process for growing and the process for growing described by Amgen in the specification. *Id.* at 9. Finally, HMR/TKT argued that even if there is literal infringement here, it can justifiably invoke the defense of the reverse doctrine of equivalents. *Id.* at 13.[12]

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[11] During the first trial, this Court found in favor of HMR/TKT on equivalent and literal infringement of the '698 patent after Amgen presented its case but before HMR/TKT had the opportunity to present its case on this issue.

[12] HMR/TKT also attempted to argue that the '698 patent should be declared unenforceable because it was obtained as a result of inequitable conduct. This Court, during the pretrial conference on September 24,

With regard to claim 7 of the '349 patent, HMR/TKT made four "new" arguments, two of which are very similar to those made in conjunction with the '698 patent. First, HMR/TKT contended that its process does not infringe claim 7 of the '349 patent when considered in light of its proposed claim construction of "DNA encoding." HMR/TKT's Mem. in Support re '698/'349 [Doc. No. 687] at 8-9. Second, HMR/TKT argued that its process does not infringe claim 7 of the '349 patent because claim 7 is a step-plus-function limitation; and, as such, HMR/TKT's process does not literally infringe the "step of culturing" found in claim 7 because it does not involve the culturing procedures set forth in Amgen's specification. *Id.* at 12-15. Third, HMR/TKT claimed that its process does not infringe the process claim under the reverse doctrine of equivalents. *Id.* at 15-18. Fourth and lastly, HMR/TKT argued that if the Court construes the term "DNA encoding" as Amgen urges, then the validity of the asserted claim of the '349 patent is called into question. *Id.* at 12.

Amgen, in response, did not dispute that "DNA encoding" needs to be construed by the Court. *See, e.g.*, Amgen's Reply re '698 [Doc. No. 731] at 6-10. It did, however, assert that HMR/TKT should not be allowed to make its "new" arguments relating to step-plus-function and the reverse doctrine of equivalents given the procedural posture of the case.[13] *See, e.g., id.* at 10-15.

2003, ruled that HMR/TKT could not put on any evidence of inequitable conduct relating to the '698 patent because it was "satisfied that the pleadings, the pretrial documents early on as to '698 did not frame that issue for trial." 9/24/03 Pretrial Conf. Tr. at 26: 4-9.

[13] Therefore, these memos requested that the Court (1) construe "DNA encoding"; (2) decide whether HMR/TKT is allowed to make its step-plus-function arguments at this stage and if yes, determine whether the asserted claims of the '349 and '698 patents are step-plus-function claims; and (3) determine whether HMR/TKT can argue the reverse doctrine of equivalents with respect to the '698 and '349 patents for the first time on remand and if so, whether this argument has merit.

On July 29, 2003, this Court held a *Markman* hearing regarding those terms in dispute and in need of construction and considered other pending motions, including motions for summary judgment. At the end of the *Markman* portion of the hearing, the Court tentatively construed the terms "DNA encoding" and "therapeutically effective," providing two constructions for the latter, one being an alternate. 7/29/03 Hr'g Tr. at 55: 1-56: 23. It then continued to hear argument. At the end of the day, the Court noted that it would determine whether the asserted claims of the '698 and '349 patents were step-plus-function claims at a later date. *Id.* at 176: 1-10. It then continued the motion hearing to July 31, 2003. *Id.* at 176: 11-15.

During a hearing two days later, the Court retracted the alternative construction and reiterated its primary "working construction," retaining its right to revise it after a more careful review of the claims, specification, and prosecution history. 7/31/03 Hr'g Tr. at 87: 5-88: 7. Additionally, it ruled that claims 4 and 6 of the '698 patent and claim 7 of the '349 patent were not step-plus-function claims pursuant to 35 U.S.C. § 112. *Id.* at 88: 8-89: 9. It then denied Amgen's motion for summary judgment of infringement of the '698 patent, citing Arthur Miller's recent article, *The Pretrial Rush to Judgment. Id.* at 89: 23-90: 25; *see* Miller, *supra.* The Court took everything else under advisement and set the final pretrial conference for September 18, 2003. *Id.* at 91: 25-92: 2.

On August 5, 2003, the Court entered an order regarding the pending motions. [Doc. No. 740]. It denied HMR/TKT's motions for summary judgment with respect to the validity of the asserted claims of the '422, '080 and '349 patents. Order of 8/5/03 at 1. It denied in part and allowed in part Amgen's motions, under Rule 52(c), for judgment that claim 1 of the '422 patent and claim 4 of the '080 patent are valid and that claims 1, 3, 4, 6, and 7 of the '349 patent are valid. *Id.* Because HMR/TKT did not dispute that the '080 and '349

patents are not anticipated by Goldwasser and that the '349 patent is not rendered obvious by Goldwasser, the Court allowed Amgen's motions with respect to these matters. *Id.* at 1-2. Specifically, the Court held that claim 4 of the '080 patent is not anticipated by Goldwasser and that claims 1, 3, 4, 6, and 7 of the '349 patent are not anticipated or rendered obvious by Goldwasser. *Id.* at 2. Because Amgen did not have the opportunity to rebut HMR/TKT's remaining validity arguments concerning the '422, '080, and '349 patents during trial in 2000, the Court stated that Amgen would have that opportunity at the October trial. *Id.*

On September 18, 2003, the Court held a final pretrial conference. After explaining that this case will not "turn into a patent version of Penelope's robe," in other words, that the Court and the parties were "not going to unravel anything [that the Court has] woven thus far which has not been unraveled by a higher court," the Court made the following findings and rulings. First, it ruled that it would hear and take evidence on the reverse doctrine of equivalents as it related to the '698 patent and that HMR/TKT could address other patent defenses. 9/18/03 Final Pretrial Conf. Tr. at 6: 4-16. Second, it ruled that Amgen had met its burden (outlined in *Festo II*) of proving that the prosecution history does not estop it from arguing equivalent infringement with regard to the '080 patent and it affirmed its earlier finding that HMR/TKT infringes claims 2-4 of the '080 patent. *Id.* at 7: 17-8: 5. It explained that it would issue a full opinion at a later date but that it might have to revisit the *Festo* issue due to the rapidly developing law in that area. *Id.* at 7: 19-25. The Court then turned to the '349 patent and explained that it would allow Amgen to put on rebuttal evidence as to the matter of obviousness and Sugimoto only and it made clear that the Court would not accept other evidence from HMR/TKT regarding the '349 patent. *Id.* at 8: 12-19, 16: 5-6 ("As far as evidence goes, '349 is in the can and I'm done with it."). The Court then issued a revised claim construction of

"therapeutically effective" based on a more thorough analysis of the claims, specification, and prosecution history. *Id.* at 9: 3-10: 25. The Court mentioned, however, that this revision may have made the third sentence of the construction unnecessary and, therefore, reserved its right to further consider the proper construction. *Id.* at 10: 21-25. It directed the parties to try the case based on the construction it had just issued along with a construction that eliminated the third sentence. *Id.* at 11: 1-5. The pretrial conference was continued until September 24, 2003. *Id.* at 30: 22-23.

During the further pretrial conference, the Court reviewed the issues to be tried and outlined the procedure for trial and the parameters for the introduction of evidence and expert testimony. *See* 9/24/03 Final Pretrial Conf. Tr. After the Court provided both parties with an opportunity to be heard on the subject, pursuant to Federal Rule of Civil Procedure 53(b)(1), the Court appointed Michele D. Beardslee as Special Master, beginning January 1, 2004, to assist the Court in research, analysis, and drafting of the forthcoming opinion. Order re Special Master [Doc. No. 801]; *see also* 11/07/03 Beardslee Aff. [Doc. No. 799].[14] The trial on remand was set to commence on October 7, 2003. 9/24/03 Final Pretrial Conf. Tr. at 40: 23.

On October 30, 2003, the Court issued an opinion supporting its ruling that Amgen had successfully rebutted the presumption of prosecution history estoppel as outlined in *Festo II* and, therefore, was not estopped from asserting

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[14] *See generally* Hon. Shira A. Scheindlin & Jonathan M. Redgrave, *Revisions in Federal Rule 53 Provide New Options for Using Special Masters in Litigation*, N.Y. St. B.A.J., Jan. 2004, at 10, *reprinted sub. nom. The Evolution and Impact of the New Federal Rule Governing Special Masters*, Fed. Law., Feb. 2004, at 35.

equivalent infringement of the '080 patent. *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 287 F. Supp. 2d 126 (D. Mass. 2003) ("*Amgen III*").[15]

The remanded trial lasted nine days over the course of four and a half weeks.[16] All the remaining issues—those remanded to the Court from the Federal Circuit and those raised by the parties in the course of this remanded trial—are addressed herein.[17]

III. CLAIM CONSTRUCTION

As expounded in great detail in *Amgen I*, this Court strongly believes in the importance of construing patent claims without regard to the alleged infringement issues. *Amgen I*, 126 F. Supp. 2d at 80-81; *MediaCom Corp.* v. *Rates Tech., Inc.*, 4 F. Supp. 2d 17, 21-24 (D. Mass. 1998); *see also* Anthony R. Zeuli & Rachel Clark Hughey, *Avoiding Patent Claim Construction Errors: Determining the Ordinary and Customary Meaning Before Reading the Written Description*,

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[15] While the reasoning need not be rehashed in this memorandum and opinion, the Court takes this opportunity to note a few typographical errors in the decision. At the following pages, the word "urinary" was inadvertently added where it should not have been: 154 ("urinary" is used five times in note 39 and should be deleted); 157 (the word "urinary" is used right before note 41 and should be deleted). As will be noted, the word "urinary" is used in many other places throughout the opinion. These uses of the word should remain. These errors do not in any way change the result of that opinion. Correction of them, however, makes the opinion more accurate.

[16] During the remanded trial, Amgen moved for Judgment Pursuant to Rule 52(c) that claims 4-9 of the '698 patent were infringed and not invalid under 35 U.S.C. § 112 [Doc. No. 778]. The Court did not rule on this motion but instead deferred entering judgment until all of the evidence had been presented. *See* Fed. R. Civ. P. 52(c). The Court's final decisions regarding infringement and validity of the '698 patent will be explained in detail below.

[17] Previous decisions by the Court, such as claim constructions, will be explained in this memorandum.

Fed. Law., June 2004, at 29. One way to avoid conflating issues of fact and law and to ensure division between the fact finding and law explaining roles in a patent case is to hold the *Markman* hearing prior to and separate from the summary judgment motion hearing. Although (as mentioned above) this Court held the *Markman* hearing for the trial on remand on the same day as the summary judgment motions hearing, it kept the hearings independent of one another by separating the hearing into two parts. The first part dealt with claim construction. Then the Court held a recess, issued its preliminary constructions, and moved on to the summary judgment motions hearing.

The Court followed its usual procedure in conducting the *Markman* hearing. The Court entertained oral argument from counsel for each party. Counsel referred the Court to the relevant portions of the patent, specification, and prosecution history. Demonstrative exhibits were presented and references were made to certain expert testimony, but extrinsic evidence was not admitted.

At the conclusion of the *Markman* portion of the hearing the Court interpreted "therapeutically effective" and "DNA encoding"—cautioning that they were "working constructions"—and held off deciding whether the asserted claims of the '349 and '698 patent were step-plus-function claims. The Court then announced during the July 31, 2003 hearing that it did not construe the asserted claims of the '349 and '698 patents as step-plus-function claims. During the pretrial conference on September 18, 2003, after the Court had engaged in a more careful review of the patents, specification, and prosecution history, the Court issued a revised claim construction for "therapeutically effective." The final claim constructions are reproduced and explained below.[18]

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[18] While the focus of the *Markman* hearing was on the patents, specification, and prosecution history, the Court writes now with the benefit

A. "Therapeutically Effective"

1. Background

The term "therapeutically effective" is contained in claim 1 of the '422 patent and claim 4 of the '080 patent.[19] As mentioned above, although this phrase was not construed during the first trial, in determining whether prior art anticipated the '422 and '080 patents, the Court interpreted the term to mean an increase in hematocrit:

> Such evidence [of e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO.

Amgen I, 126 F. Supp. 2d at 112; *see also id.* at 99 ("The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels.").

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of having presided over the entire second trial. Unsurprisingly, both parties continued to present arguments regarding construction throughout the trial, weaving in arguments regarding validity. The Court, however, construed the terms before the re-trial and, therefore, the arguments and intrinsic evidence addressed in this memorandum regarding construction of these terms stem from these data provided before the re-trial.

[19] The Federal Circuit refers to the term "therapeutically effective." The Court notes, however, that claim 1 of the '422 patent and claim 4 of the '080 patent actually recite a "therapeutically effective *amount*" of either "human erythropoietin" or "an erythropoeitin glycoprotein product," respectively. '422 and '080 Patents, Ex. 1 (emphasis added).

The Federal Circuit, in addition to remanding so that the Court could construe the term pursuant to *Markman*, provided some guidance. It agreed that the "endgame in the treatment of chronically anemic patients is to increase the hematocrit," but pointed out that the term should be construed in light of the specification. *Amgen II*, 314 F.3d at 1353. It stated, however, that the "specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy." *Id.* (citing '933 Patent, col. 33: 19-31). It pointed out that Amgen was arguing that one skilled in the art would construe "therapeutically effective" as "increasing and maintaining the patient's hematocrit to normal or near normal levels," but that "the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the specification." *Id.* at 1353-54 (citing *CCS Fitness* v. *Brunswick Corp.*, 288 F.3d 1359, 1367 (Fed. Cir. 2002) ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention.")). The Federal Circuit stated that it appeared that the term "therapeutically effective" encompassed the list of effects described in the specification and noted that if the Court also held this to be true, then the Goldwasser study may indeed invalidate some of the claims at issue in this case under 35 U.S.C. § 102(a) or § 103. *Id.* at 1354 ("If the claim term 'therapeutically effective' encompasses the patient responses described in the specification, *as it appears to us it does*, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result.") (emphasis added)). Therefore, it vacated this Court's determination that Goldwasser did not constitute prior

art[20] and ordered this Court to construe the term and thereafter determine whether Goldwasser invalidates any of the asserted patents. *Id.*

2. The Claims at Issue

The actual words of the claims are as follows:

> *'422 Claim 1*: A pharmaceutical composition comprising a *therapeutically effective* amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, where insaid erythropoietin is purified from mammalian cells grown in culture.

'422 Patent, Ex. 1, col. 38: 36-41 (emphasis added).[21]

> *'080 Claim 4*: A pharmaceutical composition comprising a *therapeutically effective* amount of an erythropoietin glycoprotein product according to Claim 1, 2, or 3.

'080 Patent, Ex. 1, col. 38: 51-53 (emphasis added).

3. Summary of the Parties' Arguments

Amgen urges adoption of the ordinary meaning of "therapeutically effective" given by those skilled in the art. Amgen's Mem. in Support re '422/'080 [Doc. No. 671] at 7. Specifically, it argues that (1) expert testimony shows that the ordinary meaning of "therapeutically effective" is "sufficient to produce a sustained increase in hematocrit," and that the term requires a therapeutic—not merely biological—effect; (2) the other effects listed in the specification, to which the Federal Circuit referred, are known biological effects of EPO, not the intended therapeutic effects; (3) the specification

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[20] The Court came to this conclusion because it found that the Goldwasser study was a failure.

[21] Although the Court did not receive evidence during the *Markman* hearing, for the sake of unity throughout this decision, citations to the patents are made to what was identified as Trial Exhibit 1 ("Ex. 1") (which contains the common specification and recitation of all the claims).

taken as a whole supports the plain meaning of "therapeutically effective," and that no special meaning was given to the term; (4) the prosecution history shows that Amgen specifically noted that its invention shares the same in vivo biological activity as naturally occurring human EPO, but differentiated its invention from prior art by pointing out that human recombinant EPO (unlike naturally-occurring human EPO) is not a viable, effective human therapeutic product; and (5) the doctrine of claim differentiation requires that this term have a different meaning than the recitation of EPO's biological activities. *Id.* at 8-17. In its reply memorandum, Amgen also argues that the dictionary definition of the term supports its asserted meaning. Amgen's Reply re '422/'080 [Doc. No. 730] at 5-6.

HMR/TKT, on the other hand, argues that the Federal Circuit made clear that it believed that the term "therapeutically effective" encompasses all of the effects set forth in the specification described. HMR/TKT's Mem. in Opp'n re '422/'080 [Doc. No. 702] at 5. Thus, it argues, the term encompasses those effects observed in the Goldwasser study. *Id.* at 6. Moreover, it asserts that Amgen is trying to import limitations from the specification to make the claims require an increase in the hematocrit levels when the claims contain no language indicating such a requirement and the specification language itself is actually inconsistent with such a requirement. HMR/TKT points to the same section of the specification as did the Federal Circuit did to make its point:

> [T]o the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates *they are conspicuously suitable for use in erythropoietin therapy procedures* practiced on mammals, including humans, *to develop any or all of the effects herefore attributed in vivo to EPO*, e.g., stimulation of reticulocyte response, development of ferrokinetic effects . . . erythrocyte mass changes, stimulation of hemoglobin

> C syntheses . . . and, as indicated in Example 10, increasing hematocrit levels in mammals.

Id. at 13 (quoting '933 Patent, Ex. 1, col. 33: 19-31). This, HMR/TKT asserts, makes clear that "erythropoietin therapy procedures" include procedures that "develop any or all of the effects heretofore attributed in vivo to EPO," and, therefore, "therapeutically effective amount" includes any or all of the effects listed in this portion of the specification—which, HMR/TKT argues, are defined in terms of biological effects. *Id.* at 14. HMR/TKT further argues that Amgen is trying to rely on isolated references of the specification to restrict the term meaning when these restrictions are not apparent in the plain language, and when the intrinsic record, as a whole, supports a broader interpretation. *Id.* at 16.

4. Discussion

While the Federal Circuit indeed mentioned that the term "therapeutically effective" appeared to encompass the biological effects listed within lines 19-31 of column 33, the Court notes that the Federal Circuit did not, in *Amgen II*, actually construe the term "therapeutically effective." *See Amgen II*, 314 F.3d at 1324 (noting that the Federal Circuit considers claim construction "afresh" on appellate review); *Bayer AG* v. *Biovail Corp.*, 279 F.3d 1340, 1349 (Fed. Cir. 2002) (noting that, notwithstanding its *de novo* review, "it would be premature for this court to engage in its own claim construction without . . . evidence of the meaning of the terms to one of skill in the art at the time of the invention"). On the contrary, the Federal Circuit remanded that task to this Court. To perform it properly, however, the Court must consider the prosecution history in addition to the claims and the specification—something that the Federal Circuit did not do. *See Amgen II*, 314 F.2d at 1324 ("To properly construe the claims, a court must examine the claims, the rest of the specification, and if in evidence, the prosecution history."); *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1582

(Fed. Cir. 1996) ("[I]t is well-settled that, in interpreting an asserted claim, the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history."); *SRI Int'l* v. *Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1118 (Fed. Cir. 1985) (noting that a claim is construed in light of its language, the specification, and the prosecution history). Moreover, the Court must begin by determining what the plain and ordinary meaning of "therapeutically effective" is in order to determine whether Amgen has become its own lexicographer. *Intellectual Prop. Dev., Inc.* v. *UA-Columbia Cablevision of Westchester, Inc.*, 336 F.3d 1308, 1315 (Fed. Cir. 2003) ("Consulting the written description and prosecution history as a threshold step in the claim construction process, before any effort is made to discern the ordinary and customary meanings attributed to the words themselves, invites a violation of our precedent counseling against importing limitations into the claims." (quoting *Texas Digital Systems, Inc.* v. *Telegenix, Inc.*, 308 F.3d 1193, 1204 (Fed. Cir. 2002)) (internal quotation marks omitted)).

a. The Plain and Ordinary Meaning

Generally, it is the plain and ordinary meaning of the words—as defined by one skilled in the relevant art—that governs. *Vitronics*, 90 F.3d at 1582; Erik Paul Belt, *Federal Circuit Stresses Ordinary Meaning*, Nat'l L.J., Sept. 22, 2003, at S1. Amgen argues that the plain and ordinary meaning of the term "therapeutically effective" is "sufficient to produce a sustained increase in hematocrit." HMR/TKT argues, on the other hand, that the plain and ordinary meaning of "therapeutically effective" is not so restricted.[22] Inter-

[22] HMR/TKT argues that Amgen's position on this claim construction is inconsistent with its position on claim construction for all the other terms the Court has construed in the previous trial because Amgen here is seeking to limit the term's definition via the specification and prosecution

estingly, HMR/TKT never states what it believes the plain and ordinary meaning of the term to be—it only discusses the meaning of the term with reference to how it believes Amgen has so defined it in the specification and prosecution history.

Amgen, on the other hand, grounds its assertion of the plain and customary meaning of the disputed term upon expert testimony. This, however, is extrinsic evidence to which resort ought be had only "*if necessary.*" *Vitronics*, 90 F.3d at 1583 (quoting *Hormone Research Foundation, Inc.* v. *Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990)). Therefore, the Court does not begin by considering this evidence. Instead, it turns first to the dictionary and to technical treatises to decipher the plain and ordinary meaning of "therapeutically effective." *See id.* at 1584 & n.6 (noting that judges are free to consult technical treatises and dictionaries

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history. HMR/TKT's Mem. in Opp'n re '422/'080 at 12. While it is true that Amgen has previously argued to the Court that the terms of the claims were entitled to their broadest possible scope, it also consistently argued that the words of the claim should prevail. *Amgen I*, 126 F. Supp. 2d at 82. In essence, it is here arguing this again. The difference is that, here, Amgen is arguing that the claim language itself contains a term that has a limited definition and that resort to the specification and prosecution history is not necessary since the plain meaning of the term prevails. HMR/TKT, on the other hand, is seeking to "broaden" what Amgen argues is the plain meaning by pointing to the specification and prosecution history.

Ultimately, how the issue has been framed will not change the analysis because it is clear from the principles of claim construction that claims are construed in light of the specification and prosecution history. *Southwall Techs., Inc.* v. *Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("The prosecution history limits the interpretation of claim terms so as to exclude *any* interpretation that was disclaimed during prosecution.") (emphasis added) (citations omitted)). Whether the Court determines that the term is limited or broadened is irrelevant. The important determinations instead are: What is the plain and ordinary meaning of "therapeutically effective," and does the intrinsic evidence define the term differently than its plain and ordinary meaning?

in order to gain a better understanding of the claims and to interpret them, "so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.").[23]

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[23] At first glance, the extrinsic evidence rule in *Vitronics* appears to create somewhat of a conundrum, in that it discourages resort to extrinsic evidence while at the same time urging courts to begin claim construction by considering the plain and customary meaning of a term *as understood by one skilled in the art*. How does a Court decipher the plain and customary meaning of a term as understood by one skilled in the art without resorting to extrinsic evidence about how one skilled in the art would construe the term?

The Federal Circuit is currently considering this question en banc. In granting a petition for rehearing en banc in *Phillips* v. *AWH Corp.*, 03-1269, -1286, the Federal Circuit asked for briefing on the following questions:

> 1. Is the public notice function of patent claims better served by referencing primarily to technical and general purpose dictionaries and similar sources to interpret a claim term or by looking primarily to the patentee's use of the term in the specification? If both sources are to be consulted, in what order?
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> 2. If dictionaries should serve as the primary source for claim interpretation, should the specification limit the full scope of the claim language (as defined by the dictionaries) only when the patentee has acted as his own lexicographer or when the specification reflects a clear disclaimer of claim scope? If so, what language in the specification will satisfy those conditions? What use should be made of general as opposed to technical dictionaries? How does the concept of ordinary meaning apply if there are multiple dictionary definitions of the same term? If the dictionary provides multiple potentially applicable definitions for a term, is it appropriate to look to the specification to determine what definition or definitions should apply?
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> 3. If the primary source for claim construction should be the specification, what use should be made of dictionaries? Should the range of the ordinary meaning of claim language be limited to the scope of the invention disclosed in the specification, for example, when only a single embodiment is disclosed and no other indications of breadth are disclosed?

> 4. Instead of viewing the claim construction methodologies in the majority and dissent of the now-vacated panel decision as alternative, conflicting approaches, should the two approaches be treated as complementary methodologies such that there is a dual restriction on claim scope, and a patentee must satisfy both limiting methodologies in order to establish the claim coverage it seeks?
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> 5. When, if ever, should claim language be narrowly construed for the sole purpose of avoiding invalidity under, *e.g.*, 35 U.S.C. §§ 102, 103 and 112?
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> 6. What role should prosecution history and expert testimony by one of ordinary skill in the art play in determining the meaning of the disputed claim terms?
>
> 7. Consistent with the Supreme Court's decision in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), and our *en banc* decision in *Cybor Corp.* v. *FAS Technologies, Inc.*, 138 F.3d 1448 (Fed. Cir. 1998), is it appropriate for this court to accord any deference to any aspect of trial court claim construction rulings? If so, in what circumstances, and to what extent?

Phillips, Order of July 21, 2004. Judge Rader, concurring in the granting of the petition, added the following:

> Is claim construction amenable to resolution by resort to strictly algorithmic rules, e.g., specification first, dictionaries first, etc.? Or is claim construction better achieved by using the order or tools relevant in each case to discern the meaning of terms according to the understanding of one or ordinary skill in the art at the time of the invention, thus entrusting trial courts to interpret claims as a contract or statute?

Id. (Rader, J., concurring).

This Court's approach is first to consider the plain and ordinary meaning as defined by dictionaries and technical treatises, and then to consider the file wrapper to determine what it communicates to the reader about the plain and customary definition of the term. It may provide clues as to how one skilled in the art would define the term or which dictionary or technical definition is adopted by those skilled in the art. Then again, it may clearly redefine the term and thus overrule the plain and ordinary meaning deciphered by the Court. Regardless, since the patent process is a public one, whatever definition is *clearly* supported in the file wrapper is the one that ought prevail, since this is the one on which the public relies. Thus, if a term supposedly has a specific technical meaning that cannot be

gleaned from general dictionaries and treatises or the file wrapper, but can only be ascertained from expert testimony, this specific meaning will not be adopted, given the *Vitronics* rule against resort to extrinsic evidence.

This Court's approach resolves the apparent conundrum by drawing a line between cognitive and investigative tasks. One can understand this process by analogizing claim construction to contract interpretation. When a judge interprets the meaning of a term in a run-of-the-mill contract, she is determining how an ordinary speaker of English would understand the term, in context, and she cannot look to extrinsic evidence unless there is some ambiguity. A dictionary constitutes extrinsic evidence of the "plain and customary" meanings that members of the relevant language community ascribe to various words, but it is also serves as a tool to enhance the judge's cognitive capacities, which capacities are then applied to the task of interpretation. In theory, at least, a judge interpreting a contract written in a foreign language would follow the same process, though she might want to gain some background understanding of the language from experts. Having acquired such background, she could then use foreign language dictionaries the same way she would use an English dictionary. Having acquired the additional cognitive capacity, the judge might find that a term's meaning is ambiguous, in which case the judge could turn to extrinsic evidence, say, of industry custom. In other words, the judge would then conduct an empirical investigation of the behavior of relevant actors.

One could thus regard the task of judges in patent cases as one of learning a number of "difficult" words in the English language, or as one of entering a new community of language. In either case, seeking "fluency" is different from determining what customs prevail in a particular "art," even if those customs involve the use of an otherwise ambiguous term. Having learned to "speak" the relevant "language" by consulting lay and technical dictionaries (and perhaps having acquired background understanding from experts), the judge can then apply these new cognitive capacities to determine whether, in context, the patent term is ambiguous. Finding that meaning, then, involves an application of the judge's enhanced cognitive abilities, not an investigation of empirical facts.

In reality, construction of patent claims does not work the same way that interpretation of foreign-language contracts does. In practice, judges interpreting foreign language contracts rely on experts to interpret them. *See, e.g.*, 1st Cir. R. 30(d) ("The court will not receive documents not in the English language unless translations are furnished."); *Ramos-Báez* v. *Bossolo-Lopéz*, 240 F.3d 92, 94 (1st Cir. 2001) (similar); *cf.* 35 U.S.C.

The dictionary definition of "therapeutic" is "[h]aving healing or curative powers," or "[o]f or relating to the treatment of disease or disorders by remedial agents or methods." *The American Heritage Dictionary* 1260 (2d college ed. 1985); W*ebster's Ninth New Collegiate Dictionary* 1223 (1984), attached as Tab X to Supp. App. [Doc. No. 735] to Amgen's Reply re '422/'080; *see also Chamber's Technical Dictionary* 844 (3d ed. 1961), attached as Tab W to Supp. App. to Amgen's Reply re '422/'080 ("Of, or pertaining to, the medical treatment of disease: remedial: curative"). The definition of therapeutics is "[t]he medical treatment of disease." T*he American Heritage Dictionary*, *supra*, at 1260. The dictionary definition of "effective" is "[h]aving an intended or expected effect" or "[p]roducing or designed to produce the desired impression or response." *Id.* at 439.

Based on these definitions alone, one would surmise that a "therapeutically effective" amount is one that produces heal-

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§ 371(c)(2) (requiring that an applicant filing a national stage application submit a copy of the international application (with certain exceptions), as well as translation into the English language of the international application). Every foreign language contract is treated as "ambiguous," because learning a new language would involve too dramatic an expansion of a judge's cognitive capacities, and an empirical investigation is the best that she can do (although once that investigation reveals which English translation is correct, the judge can then determine whether that translated document is ambiguous). The Federal Circuit has decided, however, that learning the meaning of technical terms in English, or mastering the language used by members of a community of English-speaking persons of ordinary skill in a particular art, does not reach that level. The task of claim construction falls on the "cognitive" side of the divide between expanding and applying cognitive capacities, on the one hand, and investigating empirical facts, on the other. Thus, only when application of the judge's newly acquired cognitive capacities determines that a term's meaning is ambiguous does she then turn to empirical investigation of the behavior of persons skilled in the art. She then uses dictionaries, expert testimony, and so on not as a cognitive tool, but as evidence.

ing or curing as it relates to medical treatment of disease.[24] This is, in essence, consistent with the definition that Amgen proposes. *See* Amgen's Mem. in Support re '422/'080 [Doc. No. 671] at 14 (arguing that the ordinary meaning is an amount sufficient to "cure or relieve a disease state" and "require[s] a meaningful benefit to the health of patients"). Amgen, however, goes further, asserting that the plain and ordinary meaning of "therapeutically effective amount," to one skilled in the art, taken in the context of this patent, is an amount that provides more than the biological effects of EPO and "produce[s] a sustained increase in hematocrit," because only this result provides a meaningful benefit to the health of patients suffering from anemia.[25] *Id.* at 7-8, 14. Neither the claims, the specification, nor the prosecution history, however, demonstrate clearly that the plain and ordinary meaning of the term to one skilled in the art involves an increase in hematocrit. Therefore, the Court begins with the assumption that the plain and ordinary meaning of "therapeutically effective amount" is one in line with that found in the dictionaries and treatises noted above—i.e., one that heals or cures as it relates to medical treatment of disease.

The next step is to look to the claims, specification, and prosecution history to see if Amgen redefined the term in the file wrapper. In addition, the Court will look to these sources to determine whether the file wrapper indicates clearly the types of patients for which this product is "therapeutically effective" and thus infuses the term with real meaning. In-

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[24] To heal means "[t]o restore to health, or soundness; cure." *The American Heritage Dictionary*, *supra*, at 599.

[25] This was the meaning of the term that this Court essentially adopted in its previous opinion. It was founded on expert testimony demonstrating that those skilled in the art would define "therapeutically effective"—as it relates to treating anemia—as an increase in hematocrit. Again, however, resort to such extrinsic evidence ought be had only "*if necessary*." *Vitronics*, 90 F.3d at 1583 (quoting *Hormone*, 904 F.2d at 1562).

deed, this is the elephant in the room. Without tackling this question, the term "therapeutically effective" or "therapeutically effective amount" is vague and meaningless. The public must know upon reading the patent what disease state is cured or healed by the product.[26] As the Federal Circuit pointed out, "indiscriminate reliance on definitions found in dictionaries can often produce absurd results. . . . One need not arbitrarily pick and choose from the various accepted definitions of a word to decide which meaning was intended . . . . The subject matter, the context, etc., will more often than not lead to the correct conclusion." *Renishaw PLC* v. *Marposs Societa per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (quoting *Liebscher* v. *Boothroyd*, 258 F.2d 948 C.C.P.A. 1958)) (first alteration in original). Thus, the Court, in addition to determining whether Amgen has expanded or confined the meaning of the disputed term, will look to the file wrapper to clarify this ambiguity.

b. The Claims

"The name of the game is the claim." *Amgen I*, 126 F. Supp. 2d at 80 (quoting Giles S. Rich, *Extent of Protection and Interpretation of Claims—American Perspectives*, 21 Int'l Rev. Indus. Prop. & Copyright L. 497, 499 (1990)) (internal quotation marks omitted). Thus, the first step in claim construction is to look to the plain and ordinary meaning of the words of the patent claim to determine the meaning of a term. *Vitronics*, 90 F.3d at 1582; *Bell Communications Research, Inc.* v. *Vitalink Communications Corp.*, 55 F.3d 615, 619-20 (Fed. Cir. 1995); *Renishaw*, 158 F.3d at 1248 ("[T]he claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim. . . . [T]he resulting claim interpretation must, in the

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[26] As will be noted *infra*, it appears that the patent examiner also believed that the patent needed to address for what disease states the product was "therapeutically effective."

end, accord with the words chosen by the patentee to stake out the boundary of the claimed property.").

Do the claims redefine the plain and ordinary meaning of the terms used? Amgen asserts that the claims do not support HMR/TKT's argument that it has redefined the term to include the biological effects of EPO. Amgen asserts that because claim terms are construed to give each term meaning, *Lantech, Inc.* v. *Keip Mach. Co.*, 32 F.3d 542, 546 (Fed. Cir. 1994), the patent claims themselves distinguish between biological and therapeutic effects. Amgen's Reply re '422/'080 at 10. To make its point, it refers to claims 4 and 2 of the '080 patent.

> *'080 Claim 4*: A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.
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> *'080 Claim 2*: An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

Amgen asserts that under the doctrine of claim differentiation, claim 4 of the '080 patent must not include any or all of the effects listed in the specification because otherwise claim 4 would be identical to that of claim 2. Specifically, it points out that claim 4 of the '080 patent requires "[a] pharmaceutical composition comprising a therapeutically effective amount" of EPO according to claim 1, 2, or 3. Amgen's Mem. re '422/'080 at 15-16. It then asserts that the claim 2 requires the "in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." Therefore, if "therapeutically effective" included the effects listed in the specification to which the Federal Circuit pointed, Amgen argues, it would include the in vivo

biological activity cited by claims 1, 2, or 3 of the '080 patent and render claim 4 of the '080 patent superfluous. *Id.* at 16.

As HMR/TKT urges, however, this argument is flawed because claim 4 concerns a *pharmaceutical composition* comprising a "therapeutically effective amount" of an *EPO* that happens to have the qualities described in claim 2. HMR/TKT's Opp'n re '422/'080 at 22. HMR/TKT correctly points out that claim 2 recites an isolated EPO glycoprotein and therefore refers to biological effects whereas claim 4 recites a pharmaceutical composition and involves therapeutic effects. *Id.* at 21-22. Hence, claim 2 would not be rendered superfluous if this Court construed "therapeutically effective" to include the biological effects listed in the specification. *Id.* at 22.

Another equally flawed argument is that claim 4, by encompassing claim 2 (in referring to a "therapeutically effective" amount of the product claimed in claim 2), indicates that a "*therapeutically effective* amount" is one that does more than cause the in vivo biological activities described in claim 2. After a careful review of the technology and its history, it is clear that this is not a correct reading of the claims. This review relied on extrinsic evidence, as is permissible under Federal Circuit precedent. *Vitronics*, 90 F.3d at 1584 (noting that a court may resort to extrinsic evidence and expert testimony to help it understand the technology); *Altiris, Inc.* v. *Symantex Corp.*, 318 F.3d 1363, 1371 (Fed. Cir. 2003) ("In this regard, the expert testimony serves the permissible purposes of aiding our understanding of the technology and in helping us view the patent through the eyes of the skilled artisan.").[27]

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[27] Amgen argues, based on *Altiris*, that it can rely on expert testimony to confirm the plain and customary meaning of the word as understood by one skilled in the art. HMR/TKT argues that Amgen is using the expert testimony to change the ordinary meaning of a claim term. HMR/TKT's

Before Amgen's invention, human EPO was known to elicit certain biological effects, but it was impossible to extract an efficient amount of it for use in treatment of patients with anemias and other low red blood cell disorders. Amgen invented a product, recombinant EPO, that had the same in vivo biological effects as natural EPO but differed in its carbohydrate composition and was capable of manufacture in quantities large enough to provide effective treatment.

With this understanding of the technology, it is clear that claims 2 and 4 of the '080 patent, by themselves, do not define "therapeutically effective" beyond its plain and ordinary meaning, nor do they indicate that a "therapeutically effective amount" of EPO is one that does more than elicit the biological effects noted in claim 2. Instead, claim 2 stakes out Amgen's novel recombinant EPO that has the same in vivo biological activities of natural EPO (causing bone marrow cells to increase production of reticulocytes and red blood cells). Claim 4 sets out a pharmaceutical composition that has a novel amount of the EPO—an amount that can actually treat or cure patients. Notably, these claims do not indicate whether biological effects are themselves sufficient to treat or cure patients.

Similarly, the claims of the '422 patent do not define a "therapeutically effective amount" as one that does something above and beyond eliciting the biological effects of EPO listed in the specification.

The next question is whether the claims themselves indicate for what types of patients this product is "therapeutically

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Mem. in Opp'n re '422/'080 at 19. While the expert testimony does support the plain and ordinary meaning of the term since it defines what "cure" means in the context of anemia patients, the Court will not rely on it to construe the claim, because even the *Altiris* court made clear that it was looking to expert testimony merely to understand the technology—not to construe the term itself.

effective." Amgen contends that its EPO is specifically designed for those suffering from anemias and thus only an increase in hematocrit is "therapeutically effective." Indeed, the record shows that Amgen's product *can* be used to increase levels of hematocrit, in other words, it *can* be used to "cure" or "relieve" the diseased state brought on by anemia. *Amgen I*, 126 F. Supp. 2d at 99 ("The therapeutic effectiveness or benefit of an erythropoietin preparation is shown by demonstrating a correction in anemia by increasing and maintaining the hematocrit of a patient to normal or near normal levels.").[28] Dr. Erslev testified at the first trial that a sustained increase in hematocrit and hemoglobin is required to determine whether or not anemia has been corrected. Erslev Test., Trial Tr. at 1688: 14- 1689: 4; Means Test., Trial Tr. at 1905: 17-20; 1910: 9-13. Dr. Erslev also testified that the other effects listed in the specification such as an increase in reticulocyte count or an increase in iron uptake cannot—each standing alone—correct anemia. Erslev Test., Trial Tr. at 1688: 14-1689: 4.

The problem with Amgen's argument, however, is that the claims that contain the disputed term do not themselves include a limitation directed to the specific clinical benefit of correcting *anemia*. Therefore, the plain and ordinary meaning of "therapeutically effective" cannot be limited to curing *anemia*, i.e., producing an increase in hematocrit levels based on the claims alone. The claim language simply does not allow for such a specific interpretation. This conclusion is further supported by the fact that claim 6 of the '080 patent (unlike claim 4) does indeed specify the type of treatment

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[28] While the Court cannot rely on expert testimony to help construe the term "therapeutically effective" unless absolutely necessary, it may look to the expert testimony to better understand the technology. *Vitronics*, 90 F.3d at 1584; *Altiris*, 318 F.3d at 1371. In this respect, the expert testimony that Amgen offers helps the Court understand what is necessary in order to "cure" the effects of anemia.

(kidney dialysis) for which the EPO should be used and calls out, in that context, that an effective amount is one that increases hematocrit:

> *'080 Claim 6*: A method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 4 in an amount effective to increase the hematocrit level of said patient.

'080 Patent, Ex. 1, col. 38: 57-60. Had Amgen used similar claim language in claim 4—that is, had it referred specifically to anemia—then its argument would have merit. Based on the nonspecific language of claim 4, however, this argument fails.

In sum, the claim language supports only the plain and ordinary definition of "therapeutically effective"—an amount that produces a result that, in and of itself, helps to heal or cure. The language of the claims at issue does not delineate the type of disease for which the EPO is "therapeutically effective." Therefore, the Court must now turn to the specification and the prosecution history to determine whether Amgen has limited or altered the plain meaning of the term either by defining the term or specifying the disease states for which the product is intended.

c. The Specification

The second step in claim construction is to review the specification to determine whether the patentee has used terms in a manner inconsistent with the ordinary meaning or has become his own lexicographer. *Vitronics*, 90 F.3d at 1582. In essence, "[t]he specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id.* (noting that the specification is "the single best guide to the meaning of a disputed term"). The Federal Circuit has stated that "a claim must be read in view of the specification of which it is part," and therefore, a court can use the written description to define a

term that is already in a claim limitation. *Renishaw*, 158 F. 3d at 1248; *SciMed Life Sys.*, v. *Advanced Cardiovascular Sys.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001) (noting that claims can be given a narrow construction in light of the written description and explaining that one reason to look to the specification is "to determine if the patentee has limited the scope of the claims" (quoting *Watts* v. *XL Systems, Inc.*, 232 F.3d 877, 882 (Fed. Cir. 2000))).

The part of the specification to which the Federal Circuit in *Agmen II* pointed is as follows:

> Similarly, *to the extent* that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects *herefore* attributed in vivo to EPO, e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis *(see, Eschbach, et al., supra) and,* as indicated in Example 10, increasing hematocrit levels in mammals.

'933 Patent, Ex. 1, col. 33: 19-31 (emphases added).

The Court begins by analyzing whether this section defines therapeutically effective to include the effects listed above. It is undisputed that this section declares that Amgen's recombinant EPO is similar to natural EPO in that it shares some of the same in vivo activity. *Id.* at col. 33: 19-22. "*[T]o the extent*" that it does so—to the extent that it is similar to natural EPO—Amgen's EPO are "conspicuously suitable for use in erythropoeitin therapy procedures" to develop any or all of the effects that were "herefore" (before) attributed in vivo to EPO, such as the stimulation of reticulocyte response, development of ferrokinectic effects, erythrocyte

mass changes, and stimulation of hemoglobin C synthesis. What is unclear and disputed, however, is whether the section that begins with "and, as indicated in Example 10, increasing hematocrit levels in mammals" is part of the laundry list of effects previously attributed in vivo to EPO or a separate suitable use for the product. In other words, this portion of the specification can be interpreted one of the following two ways:

> 1) Amgen's EPO is "conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, . . . and, as indicated in Example 10, increasing hematocrit levels in mammals."
>
> 2) Amgen's EPO is "conspicuously suitable for" (a) "use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects herefore attributed in vivo to EPO, e.g., stimulation of reticulocyte response, . . ." *and*, (b) "as indicated in Example 10, increasing hematocrit levels in mammals."

The former interpretation—a direct quote of the specification—suggests that an increase in hematocrit level was an effect previously attributed to natural EPO and that it, along with the biological effects, are a type of effective therapy. In other words, it includes "increasing the hematocrit levels" as *one of the many effects* of EPO that were previously identified and that are now produced by this product and useful in "erythropoietin *therapy* procedures." The problem with this reading is that the intrinsic evidence (the claims, the specification, and the prosecution history) and extrinsic evidence suggest that an increase in hematocrit levels was *not* previously attributed to natural EPO.[29] In remarks following

[29] Again, extrinsic evidence is being used to understand the technology—not to define the term.

an amendment made during prosecution of the '080 patent, Amgen explained to the Patent and Trademark Office ("PTO") that Example 10 is novel in that it is the first therapeutic procedure ever practiced with EPO to demonstrate that EPO has the capacity to generate an increase in hematocrit in vivo. Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 179. The extrinsic record also suggests that an increase in hematocrit was not previously attributed to natural EPO. *Vitronics*, 90 F.3d at 1583 ("Included within an analysis of the file history may be an examination of the prior art cited therein."). Therefore, the first reading implies a factually incorrect conclusion.

The latter interpretation—and the one that the Court adopts—suggests that an increase in hematocrit is independent or different from the in vivo effects previously attributed to natural EPO. In other words, in this section, Amgen calls out that its recombinant EPO can elicit "any or all" of the effects that natural EPO does—and more. Admittedly, the use of the words "therapy procedures" supports the interpretation that a "therapeutically effective amount" encompasses an amount that would result in the biological effects because it implies that the effects are a part of therapy. That being said, however, the way in which the increase in hematocrit is set off from the rest of the language suggests that this product elicits something in addition to what the prior art elicited, something more than the biological effects. Moreover, it makes clear that "any or all" only modifies those effects previously attributed to natural EPO—not the increase in hematocrit. Indeed, if the phrase "as indicated in Example 10, increasing hematocrit levels in mammals" were merely an item in the list of "any or all of the effects herefore attributed in vivo to EPO," then the words "in mammals" would be redundant. The list of items refers to "effects herefore attributed in vivo to EPO" for "use in erythropoietin therapy procedures practiced *on mammals*", so "increasing hematocrit

levels *in mammals*" must be a second end for which Amgen's EPO is "conspicuously suitable."

This interpretation comports with the Court's understanding—developed over the course of two intensive trials—of what hematocrit actually measures. Hematocrit measures the ability of the blood to supply oxygen to the body. It indicates the relative proportion of red blood cells to the total volume of blood. By introducing additional EPO into the patient's body, a patient's hematocrit level can be increased to and sustained at or near normal levels. In other words, the blood is able to provide a steady supply of sufficient oxygen to the tissues. It is the Court's understanding that, in *most* cases, an increase in hematocrit is accompanied, if not preceded, by "any or all" of the biological effects listed in the specification.[30] In other words, this portion of the specification explains what happens when a "therapeutically effective amount" of EPO is used—that is, it produces an increase in hematocrit—along with any or all of the biological affects previously attributed to natural EPO. As will be discussed below, this reading is further supported by other parts of the specification and the prosecution history.

Therefore, while this Court agrees with the Federal Circuit that therapeutic effectiveness "encompasses the patient responses described in the specification," this part of the specification does not indicate that these biological responses are sufficient or that Amgen "broadened" the plain meaning

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[30] This is consistent with HMR/TKT's argument with respect to validity and Goldwasser that the biological effects are critical steps in the development of red blood cells, HMR/TKT's Proposed Findings of Fact after Trial [Doc. No. 807] ¶¶ 64-66, and expert testimony. Experts on both sides agree that the biological effects are surrogate markers or early indicators that a therapeutic effect will follow. Foster Test., R. Trial Tr. at 946-47, 965; Schumacher Test., R. Trial Tr. at 807: 3-5, 813: 3-18; Eschbach Test., R. Trial Tr. at 660: 22 to 661: 8, 669: 10-670: 2, 766: 4-17; Christensen Test., R. Trial Tr. at 1185: 1-17, 1186: 9-24.

of the term "therapeutically effective" to encompass the elicitation of biological effects alone regardless of whether they heal or cure. Indeed, the term "therapeutically effective" is never even mentioned in this section of the specification. While guidance as to a claim term's meaning or a claim's scope need not be provided in explicit definitional format, *SciMed Life Systems*, 242 F.3d at 1344, to alter the plain and customary meaning of a term that is not ambiguous on its face, a patentee must do so clearly and deliberately. *Renishaw*, 158 F.3d at 1249 (noting that when a patent applicant "has elected to be a lexicographer by providing an explicit definition in the specification for a claim term[,] . . . the definition selected by the patent applicant controls" as long as the patentee's lexicography is made "'with reasonable clarity, deliberateness, and precision'" (quoting *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994))); *Vitronics*, 90 F.3d at 1582; *Altiris*, 318 F.3d at 1370.[31] Here, there is no "manifest exclusion or restriction, representing a clear disavowal of claim scope." *Teleflex, Inc.* v. *Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). Thus, this portion of the specification does not redefine the plain and ordinary meaning of the term to include the biological effects regardless of whether they heal or cure. Likewise, this portion of the specification does not limit the term to an increase in hematocrit. While it makes clear that its product is useful

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[31] This is not to suggest that the specification cannot provide guidance as to the scope of the claims absent a clear and deliberate act of lexicography by the patentee. Indeed, if the claim's scope cannot be ascertained from the ordinary and plain meaning of the words alone, the specification can assist and even limit the interpretation of the claims. *Teleflex, Inc.* v. *Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002). The relevant portion of the specification, however, does not indicate that the patentee deliberately altered the meaning of "therapeutically effective," and indeed the term at issue is not ambiguous. As will be discussed below, what is ambiguous is for whom the invention is intended to be "therapeutically effective."

because it can increase hematocrit, it does not redefine the term in question to equate only with an increase in hematocrit (or relate only to curing anemia).

Amgen points to a few other portions of the specification in support of its argument that while it did not alter the meaning of "therapeutically effective" to include the biological effects, it did limit the claimed therapy to patients suffering from anemia and anemia-like disorders and likewise limited the claim to an increase in hematocrit.[32]

The first such passage is the one immediately following the portion of the specification cited by the Federal Circuit:

> *Included within* the class of humans treatable with products of the invention are patients generally requiring blood transfusion and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

'933 Patent, Ex. 1, col. 33: 31-36 (emphasis added).[33] As HMR/TKT correctly points out, this list of patients is obviously incomplete as it begins with the words "included within," which suggests that there are other types of patients for which the product is intended. HMR/TKT's Post-Hr'g Mem. [Doc. No. 747] at 4. While this is true, it still provides insight into the type of patients who may receive a therapeutic benefit from the pharmaceutical compositions of the invention. Therefore, while the specification does not actively limit

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[32] If Amgen limited the invention to patients suffering from anemia, then by default the definition of "therapeutically effective" equates with an increase in hematocrit *if* only an increase in hematocrit heals or cures anemia.

[33] All of these patients are in many respects transfusion-dependent. Extrinsic evidence demonstrates that it is an increase in hematocrit which eliminates the need for transfusions.

the term to this class of patients, it provides guidance to the Court in defining the term. *Vitronics*, 90 F.3d at 1582; *Teleflex, Inc.*, 299 F.3d at 1325 ("The specification may assist in resolving ambiguity where the ordinary and customary meaning of the words used in the claims lack sufficient clarity to permit the scope of the claim to be ascertained from the words alone."). By listing the types of patients responding to treatment by the product, the specification implies that the term "therapeutically effective" amount was written with respect to these types or classes of patients. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by *implication*." *Vitronics*, 90 F.3d at 1582 (emphasis added).[34] It does not, however, indicate that this invention is only for the treatment of anemia but instead for all the ailments listed. While this may not be an exhaustive list and patients with similar or like disorders might also benefit from the product, this list begins to infuse "therapeutically effective amount" with real meaning.

Other portions of the specification support interpreting the claims with reference to the class of patients listed in the specification. For example, the specification states: "The minimization of the need for transfusion therapy through use of EPO therapy can be expected to result in reduced transmission of infectious agents." '933 Patent, Ex. 1., col. 33: 37-39. While this is only one example of how the product

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[34] If this were not the case, arguably, the patent would be invalid for indefiniteness. Issued patents are presumed to be valid, 35 U.S.C. § 282; *National Recovery Techs., Inc.* v. *Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195 (Fed. Cir. 1999), and "claims should be construed to sustain their validity," *Rhine* v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999); *see also Amgen I*, 126 F. Supp. 2d at 83. The Court need not address, however, whether the likelihood that a broad construction would render the '933 patent invalid is significant enough to provide an alternative justification for the narrower construction on which the Court has settled.

is useful or advantageous, it falls within the class of patients listed in the specification.[35]

Other pertinent sections are as follows:

> It has recently been estimated that the availability of erythropoietin in quantity would allow for treatment each year of anemias of 1,600,000 persons in the United States alone.

Id. at col. 6: 35-39.

> . . . clinical testing and potential wide-ranging *therapeutic use* of [Lin's recombinant EPO] in treatment of e.g., chronic kidney disease wherein diseased tissues fail to sustain production of erythropoietin.

Id. at col. 9: 6-9 (emphasis added).

> *Also* comprehended by the invention are pharmaceutical compositions comprising effective amounts of polypeptide products of the invention together with suitable diluents, adjuvants and/or carriers which allow for provision of erythropoietin therapy, *especially in* the treatment of anemic disease states and most especially such anemic states as attend chronic renal failure.

Id. at col. 12: 1-7 (emphasis added).

> Because erythropoietin is essential in the process of red blood cell formation, the hormone has potential useful

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[35] Amgen argues that the "minimization of the need for transfusion therapy"—which is used to increase the oxygen transport capacity of the blood—can only be achieved by raising an anemic patient's hematocrit for a sustained period. Amgen's Mem. in Support re '422/'080 at 12. Therefore, it argues that this section supports its contention that the term "therapeutically effective" means an increase in hematocrit. *Id.* This section, however, is merely explicating one example of how the product is useful or advantageous—just as the section on the class of patients included patients suffering from anemias that can be cured by an increase in hematocrit but also included patients in need of blood transfusions.

> application in both the diagnosis and the *treatment* of blood disorders characterized by low or defective red blood cell production.

Id. at col. 6: 20-24 (emphasis added).[36]

Amgen also points to column 6, lines 28-33 of the '933 patent, which cites a study done by Eschbach:

> *See*, generally, . . . Eschbach, et al[.] . . . describing a therapeutic regimen for uremic sheep based on in vivo response to erythropoietin-rich plasma infusions and proposing a dosage of 10 U EPO/kg per day for 15-40 days as corrective of anemia of the type associated with chronic renal failure.

That Amgen intended its invention to treat anemic patients is clear from these sections (along with the prosecution history, as will be discussed below) and is pertinent to the analysis. *Renishaw*, 158 F.3d at 1250 (noting that what the "inventors actually invented and intended to envelop with the claim" is relevant in claim construction); *CVI/Beta Ventures* v. *Tura LP*, 112 F.3d 1146, 1160 (Fed. Cir. 1997) ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration."). None of these sections, however, shows that Amgen intentionally re-defined the plain meaning of the term "therapeutically effective" to refer exclusively to anemia or to an increase in hematocrit.

While these sections do not suggest that the product is solely intended for anemic patients and to increase hematocrit, they do imply, in combination, that it is designed for

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[36] As will be discussed *infra*, the extrinsic evidence shows that an increase in hematocrit is necessary to cure defective red blood cell production effectively.

the class of patients listed in column 33 and noted above.[37] That being said, it seems to stretch the doctrine of claim construction too far to incorporate into the plain and ordinary meaning a reference to a class of patients that at best is only implied in the specification. *Northern Telecom Ltd.* v. *Samsung Elecs. Co.*, 215 F.3d 1281, 1294 (Fed. Cir. 2000); *KX Indus., L.P.* v. *PUR Water Purification Prods.*, 18 Fed. Appx. 871, 876 (Fed. Cir. Aug. 10, 2001) (unpublished opinion)[38] ("[W]hat is determinative is whether the patentee has defined a claim term as excluding a broader interpretation with reasonable clarity and deliberateness."). On the other hand, it seems foolish to construe a term such as "therapeutically effective," without reference to a class of patients for which the product is intended to be "therapeutically effective." This quandary, however, is put to rest by the prosecution history. When the specification is considered along with the prosecution history, it becomes apparent that a class-of-patients limitation is appropriate.

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[37] As will be discussed at great length *infra*, if the term "therapeutically effective" is properly construed only with reference to this class of patients, it is irrelevant whether Amgen actually refined the term to mean an "increase in hematocrit" as the evidence at trial confirmed that these types of patients are only healed or cured by an increase in hematocrit and not by any of the biological effects.

[38] Citing an unpublished opinion raises a number of difficult questions. *See Anastasoff* v. *United States*, 223 F.3d 898, 899-905 (8th Cir. 2000) (Arnold, J.) (holding that unpublished opinions have precedential effect), *vacated as moot*, 235 F.3d 1054 (8th Cir. 2000) (en banc), *Giese* v. *Pierce Chem. Co.*, 43 F. Supp. 2d 98, 103 n.1 (D. Mass. 1999) (relying on unpublished opinions' persuasive authority); Hon. Richard S. Arnold, *Unpublished Opinions: A Comment*, 1 J. App. Prac. & Process 219 (1999); *see also* Proposed Fed. R. App. P. 32.1; Anne Coyle, Note, *A Modest Reform: The New Rule 32.1 Permitting Citation to Unpublished Opinions in the Federal Courts of Appeals*, 72 Ford. L. Rev. 2471 (2004). *But see* Hon. Alex Kozinski, Letter, Fed. Law., June 2004, at 37.

d. The Prosecution History

The third step in claim construction is to consider the prosecution history to determine whether the applicant has made any express representations regarding the claim's scope. *Vitronics*, 90 F.3d at 1582-83; *Standard Oil Co.* v. *American Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985) ("[A]ll express representations made by or on behalf of the applicant to the examiner to induce a patent grant . . . [can] limit[] the interpretation of claims."); *Alpex Computer Corp.* v. *Nintendo Co. Ltd.*, 102 F.3d 1214, 1220 (Fed. Cir. 1996) (noting that prosecution history is "relevant . . . for construing the meaning and scope of the claims").

The amendments made early on in pursuance of the patents support HMR/TKT's contention that Amgen defined a "therapeutically effective amount" of EPO to encompass an amount sufficient to elicit any or all of the biological effects that were attributed to natural EPO.

On December 5, 1988, in response to a rejection under 35 U.S.C. §§ 112, 102(b) and 103 of what eventually became the '080 patent, Amgen submitted independent claim 41 and dependent claims 55-57 and 61-66. The pertinent amendments are claim 41 (which relates to claim 2 of the '080 patent), claim 55 (which relates to claim 4 of the '080 patent), claim 57 (which relates to claim 6 of the '080 patent), and claim 56 (because it is referenced in claim 57).

> *Claim 41:* A glycoprotein product having a primary structural conformation and glycosylation sufficiently duplicative of that of a naturally occurring human erythropoietin to allow possession of the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and having an average carbohydrate composition which differs from that of naturally occurring human erythropoietin.

> *Claim 55:* A pharmaceutical composition comprising an effective amount of a glycoprotein product according to claim 41 and a pharmaceutically acceptable diluent, adjuvant or carrier.
>
> *Claim 56:* A method for providing erythropoietin therapy to a mammal comprising administering an effective amount of a glycoprotein product according to claim 41.
>
> *Claim 57:* A method according to claim 56 wherein the therapy comprises enhancing hematocrit levels.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 174-75.

These claims make clear that Amgen's product purposefully duplicates natural EPO in that it elicits the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, but that it differs from natural EPO in its carbohydrate composition. These claims also make clear that claim 55 (similar to claim 4 in the '080 patent) is not limited to increasing hematocrit because that is precisely what claim 57 does (and what claim 6 in the '080 patent now does). In the remarks accompanying the amendment, Amgen twice explained that its product produces the same in vivo biological activity as that of natural EPO:

> Applicant's novel glycoprotein preparations . . . hav[e] the glycosylation-requiring *in vivo* biological activity (promoting reticulocyte and red blood cell production) characteristics of naturally occurring human erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 175.

> [T]he glycoprotein products herein claimed . . . possess the essential *in vivo* biological activity of naturally occurring erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 181. It then explained, with reference to claim 56, that Amgen "first

developed knowledge of the full amino acid sequence of erythropoietin and first generated the presently claimed glycoprotien products which allowed for full scale clinical application to provide *therapeutic effects* consistent with the *in vivo* activity of naturally occurring erythropoietin." *Id.* at 177 (first emphasis added). With reference to claim 41, it stated that Amgen "was the first to provide a glycoprotein which is *both* different from previously isolated urinary erythropoietin in its glycoyslation and yet sufficiently like the natural product . . . in terms of its glycosylation to allow it to fill the long-felt need (unsatisfiable by urinary isolates) for life-sustaining human therapeutic agents for, e.g., the anemia associated with dialysis in renal failure patients." *Id.* at 178. It then explained that the product is "sufficiently like" natural EPO in glycosylation because it "allow[s] for *in vivo* biological activity." *Id.* at 179. Later, it explained that Example 10 is novel in that it is the first therapeutic procedure ever practiced with EPO to demonstrate that EPO has the capacity to generate in vivo an increase in hematocrit. *Id.*

Taken in combination, the amendments and these remarks support the interpretation that Amgen intended "therapeutically effective amounts" of EPO to encompass an amount that elicited in patients any or all of the biological effects previously attributed to natural EPO and that it did not limit the term to an increase in hematocrit.[39] Such an effect is separately claimed in claim 6 (here claim 57).

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[39] The specification at that time confirms this interpretation:

> Novel glycoprotein products of the invention includes those having a primary structural conformation sufficiently duplicative of that of a naturally-occurring (e.g., human) erythropoietin to allow possession of one or more of the biological properties thereof and having an average carbohydrate composition which differs from that of naturally-occurring (e.g., human) erythropoietin.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 6, at 180; *see also id.* at 181.

Were this the entire prosecution history, the Court would agree with HMR/TKT and the Federal Circuit that Amgen broadened the term to mean one that elicits any or all of the in vivo effects before attributed to natural EPO regardless of whether they actually heal or cure the patient. In the course of overcoming two additional rejections later on in the process, however, Amgen differentiated its product from natural EPO (i.e., it overcame rejection) by asserting that natural EPO—which elicits the biological effects—was not therapeutically viable, whereas its product was clinically effective and designed specifically for a class of patients for which the product was intended. In doing so, Amgen avowed that its invention produced enough quantity of EPO to elicit responses that actually healed or cured the patient. *Renishaw*, 158 F.3d at 1249 n.3 ("[A]ny interpretation that is provided or disavowed in the prosecution history also shapes the claim scope."); *Standard Oil Co.*, 774 F.2d at 452 ("[T]he prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.").

For example, in a June 5, 1989 amendment, in response to a PTO rejection under 35 U.S.C. § 103 for obviousness, Amgen distinguished its recombinant EPO product from natural EPO by claiming natural EPO was "not a viable therapeutic product" whereas its recombinant EPO was "clinically effective" and the "first therapeutic product" successfully to treat anemia and other disorders involving low red blood cell counts:

> All of the references cited by the Examiner in this rejection relate to naturally occurring erythropoietin. The claims of the subject invention relate to erythropoeitin which is produced through recombinant DNA techniques. Recombinant erythropoietin is different from naturally occurring erythropoietin. . . Moreover, natur-

> ally occurring human erythropoietin is not a viable human therapeutic product; human recombinant erythropoietin, on the other hand, has been proven to be clinically effective, *and* is the first therapeutic product which can be used to effectively treat the hundreds of thousands of patients who suffer from anemia and other disorders involving low red blood cell counts.

Amgen's '422/'080 App., Tab G (Ex. 2), at Tab 11, at 227 (emphasis omitted). Amgen further explained that "[i]n contrast to recombinant erythropoietin, naturally occurring human erythropoietin is not used to treat patients. In the past, efforts were made to obtain purified erythropoietin from natural sources . . . . The results of these efforts however yielded only a small amount of material which was far too little for clinical research." *Id.* at 229. As the FDA stated in its approval of recombinant EPO "there is not enough naturally occurring enthropoetin produced to collect it from healthy persons for use in treatment," but "gene splicing techniques have permitted its production." *Id.* Thus, in response to this rejection, Amgen differentiated its EPO from natural EPO in two respects. First, Amgen claimed its invention allowed for a sufficient amount of EPO actually to treat patients—as opposed to natural EPO which was not available in large enough quantities. Second, it claimed its EPO, as opposed to prior art, effectively treated patients suffering from anemia or other disorders involving low red blood cell count.[40] This was a clear and definitive statement about what the invention "envelopes." *Renishaw*, 158 F.3d at 1250 (noting that a term can only be properly interpreted "with a full understanding of what the inventors actually

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[40] This supports Amgen's contention that it defined "therapeutically effective" as an increase in hematocrit since, as will be discussed *infra*, the evidence shows that an increase in hematocrit—unlike the other biological effects listed in the specification—cures or heals the diseased states mentioned in the specification.

invented and intended to envelop with the claim" and that the correct construction is that which "stays true to the claim language and most naturally aligns with the patent's description of the invention"). Here, the prosecution history makes clear that Amgen intended its invention to be clinically effective at least for the class of patients suffering from anemia and low red blood cell disorders. *See Standard Oil Co.*, 774 F.2d at 452 ("[A]ll express representations made by or on behalf of the applicant to the examiner to induce a patent grant or . . . to reissue a patent . . . [can] limit[] the interpretation of claims."); *Spectrum Int'l Inc.* v. *Sterilite Corp.*, 164 F.3d 1372, 1378 (Fed. Cir. 1998) ("[E]xplicit statements made by a patent applicant during prosecution to distinguish a claimed invention over prior art may serve to narrow the scope of the claim."). Amgen was trying to cure anemia and other diseases associated with low red blood cell count—not simply to duplicate the effects of natural EPO regardless of whether those effects cured or healed. *CVI/Beta Ventures*, 112 F.3d at 1160 ("In construing claims, the problem the inventor was attempting to solve, as discerned from the specification and the prosecution history, is a relevant consideration.").

That Amgen intended its invention to provide a meaningful health benefit to the list of patients expressly mentioned in the specification is supported by another portion of the prosecution history. On November 6, 1990, Amgen claimed the following in an application that eventually resulted in the '422 patent:

> *Claim 61:* An erythropoietin-containing, pharmaceutically-acceptable composition wherein human serum albumin is mixed with erythropoietin.
>
> *Claim 62:* A composition according to claim 61 containing a therapeutically effective amount of erythropoietin.

> *Claim 63:* A composition according to claim 61 containing a therapeutically effective amount of recombinant erythropoietin.[41]

HMR/TKT's App. to Opp'n [Doc. No. 705], Tab 2 (Ex. 2003, 11/6/90 Preliminary Amendment) at 9. The examiner rejected claims 62 and 63 as "being indefinite for failing to particularly point out and distinctly claim the subject matter which [the] applicant regard[ed] as the invention." *Id.* (Ex. 2003, 6/1/94 Examiner's Action) at 2. Claim 62 was rejected for being "vague and indefinite because it is unclear what the claimed composition is required to be 'effective' for," and claim 63 was rejected as "vague and indefinite because it is unclear as to how the recitation that the claimed erythropoietin is 'recombinant' modifies the physical erythropoietin composition[;] . . . while the claimed erythropoietin may be prepared using recombinant techniques, the product would not necessarily distinguish over that found in nature." *Id.* In essence, then, the examiner rejected Amgen's patent because it did not specify for what type of patients the product was intended to be "therapeutically effective" *and* it did not distinguish how the recombinant EPO was different than natural EPO besides its preparation. In other words, it did not differentiate what recombinant EPO provided to patients that natural EPO did not.

Amgen requested reconsideration, stating that the terms "effective" and "recombinant" are, "in view of the extensive disclosure of the specification," well-defined and understood by a person of skilled in the art. *Id.* (Ex. 2003, 12/1/94 Request for Reconsideration) at 1. Amgen argued that "the specification indicates *several potential therapeutic uses* for the claimed invention." *Id.* at 2 (emphasis added). It then

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[41] These were the original claim numbers in the application 08/100,197 for what is now the '422 patent. Also, the word "composition" was crossed out and handwritten above it was the word "preparation."

quoted the exact portion of the specification to which the Federal Circuit had pointed, where the in vivo effects along with the effect of an increase in hematocrit levels are mentioned. *Id.* Importantly, however, Amgen also quoted the following sections regarding the class of humans treatable with products:

> Similarly, to the extent that polypeptide products of the invention share the in vivo activity of natural EPO isolates they are conspicuously suitable for use in erythropoietin therapy procedures practiced on mammals, including humans, to develop any or all of the effects heretofore attributed in vivo to EPO e.g., stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (*see, Eschbach, et al*[.], *supra*) and[,] as indicated in Example 10, increasing hematocrit levels in mammals. Included within the class of humans treatable with products of the invention are patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias[,] and the like.

Id. (Ex. 2003, 12/1/94 Request for Reconsideration) at 2 (emphasis omitted) (quoting '933 Patent, Ex. 1, col. 33: 19-36). According to Amgen,

> these sentences from the specification and others provide a clear and definite description of the *uses for which the claimed erythropoietin compositions would be therapeutically effective*. A person of skill in the art would understand that the amount of erythropoeitin necessary to achieve these defined therapeutic results would vary for each use. However, *clinicians can readily determine*

> *the "therapeutically effective" amounts for each condition, and indeed for each patient.*

Id. (emphasis added).

The question then is what are the "uses" to which Amgen refers. At first blush, it may appear that the "therapeutic uses" are the effects listed in the specification. A close reading of the remarks, however, makes clear that the words "uses" and "use" refer to treatment of the conditions listed in the specification—not to eliciting the effects. If this were not the case, the following sentence would not make sense: "A person of skill in the art would understand that the amount of erythropoeitin necessary to achieve these defined therapeutic results would vary for each *use*." *Id.* (emphasis added). Amgen overcame a rejection of indefiniteness, in part by claiming that its product was specifically designed to treat patients suffering from the types of disease listed in the specification. Such a clear avowal—when considered alone or along with the other parts of the prosecution history and specification—would estop Amgen now were it to try to claim that its product was "therapeutically effective" in treating patients with *high* red blood cell counts. *Alpex Computer Corp.*, 102 F.3d at 1221 ("Just as prosecution history estoppel may act to estop an equivalence argument under the doctrine of equivalents, positions taken before the PTO may bar an inconsistent position on claim construction."); *Ekchian* v. *Home Depot, Inc.*, 104 F.3d 1299, 1304 (Fed. Cir. 1997) ("[B]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, [and] he is by implication surrendering such protection."). Here we have prosecution history estoppel in reverse—that is, Amgen wants this Court to constrain the meaning of the term to this class of patients. This does not change the effect the Court must give Amgen's clear and definite statements. Thus, the Court holds that Amgen limited the term in dispute to refer to the class of

patients listed in the specification and quoted to the examiner. *Telefex*, 299 F.3d at 1327 (noting that a term can be limited or extended by the specification or prosecution history as long as the patentee *clearly* intended to do so); *Altiris*, 318 F.3d at 1370 (same).[42]

The trickier question, however, is whether these remarks define the disputed term to include the in vivo effects of EPO *regardless* of whether they heal or cure this class of patients.[43] While it is a close call, the Court does not so read these remarks. Admittedly, all of the effects—the in vivo effects and an increase in hematocrit—are labeled together as "therapeutic results." What is not made clear, however, is whether "therapeutic results" equates with "therapeutically effective." While there is support for reading the terms as coextensive, there is also support for viewing them differently. Amgen specifically differentiates between an amount that achieves therapeutic *results* and a "therapeutically effective amount:"

> A person of skill in the art would understand that the *amount* of erythropoeitin necessary to achieve these defined therapeutic results would vary for each use. However, clinicians can readily determine the *"thera-*

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[42] While "it is improper for a court to add extraneous limitations to a claim," *Hoganas AG* v. *Dresser Indus., Inc.*, 9 F.3d 948, 950 (Fed. Cir. 1993), this limitation, as explained earlier, is not "extraneous." Without a limitation regarding the class of patients to which recombinant EPO is useful, it is impossible to "interpret what the patentee meant" by the disputed term.

[43] As with the specification, these remarks make clear that any or all of the biological effects are part and parcel of therapeutic effectiveness, that is, that Amgen refined "therapeutically effective amount" to be one that, at the least, elicits one or more of the in vivo effects heretofore attributed to natural EPO.

> *peutically effective"* amounts for each condition, and indeed for each patient.

HMR/TKT's App. to Opp'n, Tab 2 (Ex. 2003, 12/1/94 Request for Reconsideration), at 2 (emphasis added). These two sentences indicate that a different amount of EPO is used to achieve each of the effects listed in the specification—including the in vivo effects—depending on the condition and needs of the patient, *but* that a clinician can determine the amount that would be "therapeutically effective." Thus, when read together, these sentences indicate that (1) the biological effects listed in the specification are part of the "therapy" but not necessarily "therapeutically effective," i.e., they do not necessarily heal or cure the patient, and (2) the amount necessary for therapeutic effectiveness—an amount that heals or cures—depends on the types of patients to which the recombinant EPO is being administered.

Because these remarks do not clearly disavow the ordinary and customary meaning of the disputed term and can actually be interpreted to support the ordinary and customary meaning of the disputed term,[44] the Court does not construe "therapeutically effective" to encompass any or all of the biological effects regardless of whether they work to heal or cure. *Amgen II*, 314 F.3d at 1327 ("We indulge a heavy presumption that a claim term carries its ordinary and customary meaning . . . [P]rosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage."); *see KX Industries, L.P.* v. *PUR Water Purification Prod.*, 18 Fed. Appx. 871, 876 (Fed. Cir. 2001) (unpublished opinion); *see also Northern*

[44] Although the Court does not read them as such, these sentences *could* be interpreted to support that "therapeutically effective" includes the biological effects. This ambiguity, however, does not establish HMR/TKT's point. To the contrary, it demonstrates that the patentee did not clearly and deliberately redefine the term and that the plain and ordinary meaning should prevail.

Telecom Ltd. v. *Samsung Elec. Co.*, Ltd, 215 F.3d 1281, 1294-95 (Fed. Cir. 2000) (analyzing whether the patentee in the prosecution history "with reasonable clarity and deliberateness" excluded a broader interpretation of the claims).[45] In further support of this conclusion is the fact that the examiner allowed the claims to stand. As the Federal Circuit pointed out in a slightly different context in *Amgen II*, "[w]e must presume the examiner did his job, and if he truly thought that" Amgen's EPO was the same as natural EPO in that it merely elicited the biological effects, "the asserted claims would not have issued." 314 F.3d at 1327.[46]

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[45] This ambiguity itself is helpful to Amgen, given that "claims should be construed to sustain their validity" and Amgen is not advancing a definition of the term that is contrary to the plain and ordinary meaning. *Rhine* v. *Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999); *see also Amgen I*, 126 F. Supp. 2d at 83 ("[T]he canon that claims terms ought be construed to sustain their validity is simply an interpretation tool to aid courts in determining what a reasonably disputed claim term means in light of the specifications."). If the Court were to construe the term as HMR/TKT urges—as covering mere biological responses—the claims would likely be invalid as anticipated by prior art.

[46] Further support for the conclusion that Amgen was not redefining therapeutic effectiveness to include the biological effects regardless of whether they worked to heal or cure the patient is found in the prior art disclosed to the patent examiner. *Autorigo Co. of America* v. *United States*, 384 F.2d 391, 399 (Fed. Cir. 1967) ("In its broader use as source material, the prior art cited in the file wrapper gives clues as to what the claims do not cover."). Although it appears Amgen did not cite the Goldwasser study, it did disclose it to the examiner. *Amgen I*, 126 F. Supp. 2d at 138-39. As will be discussed *infra*, Dr. Goldwasser obtained a preparation of highly purified EPO derived from human urine. *Amgen I*, 126 F. Supp. 2d at 111-112. He administered EPO to three anemic patients and reported an increase in reticulocyte count in all three patients, an increase in erythroid cells in marrow and increased plasma iron clearance rate in two patients, and an increase in red cell mass in one patient. *Id.* Dr. Goldwasser admitted that there was no significant change in the hematocrit levels of any of the patients and as such, the trial was a failure. *Id.* The fact that Dr. Goldwasser believed his study to be a failure, that is,

5. Conclusion and Claim Construction of "Therapeutically Effective"

The Federal Circuit has stated that "any interpretation [of a patent claim term] that is provided or disavowed in the prosecution history shapes the claim scope." *Renishaw*, 158 F.3d at 1243 n.3; *see Digital Biometrics, Inc.* v. *Identix, Inc.*, 149 F.3d 1335, 1347 (Fed. Cir. 1998) ("The public has a right to rely on such definitive statements made during prosecution."); *Ekchian*, 104 F.3d at 1303-04 (noting that the courts and the public may rely on an information disclosure statement to interpret a claim). Here, to overcome a patent rejection for indefiniteness, Amgen avowed that its invention was "therapeutically effective" for the class of patients listed in column 33 of the specification. Therefore, the Court rules that "therapeutically effective" must be read with reference to this class of patients despite the fact that the specification uses the words "included within." Amgen did not, however, go so far as to limit the list of patients to those suffering from anemia only or refine the term to mean an increase in hematocrit.[47] Nor did Amgen clearly redefine the term "thera-

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that it did not provide a meaningful health benefit to patients when it achieved the biological effects of EPO but not an increase in hematocrit indicates that Amgen's claims are not merely covering the biological effects.

[47] While the specification and prosecution history support Amgen's contention that it defined "therapeutically effective" to mean an increase in hematocrit, the intrinsic evidence does not show a *clear* and *deliberate* attempt to redefine the term this way. Even were this not the case, and the Court ruled there was a clear and deliberate intent to define "therapeutically effective" as an increase in hematocrit—or for that matter had resorted to extrinsic evidence and ruled that this was how those skilled in the art defined the term—the end result regarding validity of these patents in view of prior art would not be different. As will be discussed further below, the evidence shows that the biologic effects of EPO do not elicit any meaningful health benefit to patients. Therefore, the only thing claimed in the patent that actually does heal or cure is an increase in

peutically effective amount" to mean an amount that induces the effects heretofore attributed to natural EPO regardless of whether they work to heal or cure the patient. To the contrary, Amgen repeatedly states in the prosecution history and in the specification that recombinant EPO's novelty is that it can actually effectively treat, that is heal or cure, patients. While "the inventor's subjective intent as to claim scope, *when unexpressed in the patent documents*, [should not] have any effect," *Vitronics*, 90 F.3d at 1584 (emphasis added), the correct construction is that which "stays true to the claim language and most naturally aligns with the patent's description of the invention," *Renishaw*, 158 F.3d at 1243. Throughout the prosecution history, Amgen repeatedly describes the invention as one that *heals* patients suffering from low red blood cell counts—something that could not be done

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hematocrit. Thus, by default the terms "therapeutically effective" and "increase in hematocrit" become synonymous.

As mentioned earlier, an alternate route would have been to consider extrinsic evidence as to the meaning those skilled in the art would give the disputed term. Indeed, much evidence was presented at the first trial on the subject, the bulk of which supports Amgen's contention that one skilled in the art would equate "therapeutically effective" with an increase in hematocrit when considering anemia. Two crucial witnesses for the defense conceded as much. Dr. Means testified that in the routine practice of medicine as it relates to EPO in treating anemia in patients, "an increase in hematocrit is how one defines a response." Means Test., Trial Tr. at 1910: 9-13. Dr. Erslev agreed that the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit. Erslev Test., Trial Tr. at 1675: 12-23. The only problem with relying on such evidence—other than the Federal Circuit's ruling in *Vitronics* and the concern for public reliance on the record—is that this expert testimony was given in reference to anemic patients specifically and did not take into account the entire list of patients in the specification.

In hindsight, however, it appears that this distinction between anemia and the entire list of patients included in the specification is meaningless, for the evidence shows that only an increase in hematocrit provides a meaningful health benefit to the class of patients listed in the specification.

before. While the prosecution history and specification indicate a clear intent to define "therapeutically effective amount" as one that elicits "one or more" of the in vivo effects of natural EPO, they do not define the in vivo effects as *necessarily* being "therapeutically effective." In other words, they do not define these effects as being "therapeutically effective" regardless of whether they heal or cure. Instead, the plain and ordinary meaning of the term "therapeutically effective amount" was refined to (1) *require* (in addition to healing or curing) an elicitation of one or more of the in vivo effects that was attributed to natural EPO and (2) be read in the context of a certain class of patients. Thus, the Court's claim construction is as follows:

> A therapeutically effective amount is a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that elicits in vivo biological activity of natural EPO such as those listed in the specification, column 33, lines 24 through 28: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis (*see, Eschbach, et al., supra*) and, as indicated in Example 10, increasing hematocrit levels in mammals.
>
> Therapeutically effective is to be interpreted as being therapeutically effective with respect to the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like.

See 9/18/03 Pretrial Conference Tr. at 9-11.

As will be discussed further below, in deciding whether the Goldwasser reference anticipates Amgen's patents, this construction leaves the Court with a very fact-intensive task: determining which, if any, of the effects listed in the specification actually heal or cure the class of patients referred to therein.

B. "DNA Encoding"

1. Background

At the close of Amgen's case-in-chief during the first trial, this Court granted HMR/TKT's Fed. R. Civ. P. 52(c) motions for judgment of non-infringement of claims 4-9 of Amgen's '698 process patent. *Amgen I*, 126 F. Supp. 2d at 99-101. On appeal, the Federal Circuit vacated and remanded this Court's rulings regarding infringement of the '698 patent because the Court had compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347.

In the memoranda in support and in opposition to each party's motions regarding infringement of the '698 patent, the parties argued different interpretations of the term "DNA encoding" found in claims 4 and 6 of the '698 patent. Thus, the Court concluded that the term is in dispute and needed to be construed in order properly to determine the issue of literal infringement.[48]

2. The Claims at Issue

Claim 4 of the '698 Patent:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase

[48] Neither party objects to the Court now formally construing the term despite the fact that this issue was not raised during the first trial.

> production of reticulocytes and red blood cells comprising the steps of: (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to *DNA encoding* the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

'698 Patent, Ex. 1, col. 38: 37-47 (emphasis added) (paragraph structure altered).

> *Claim 6 of the '698 Patent*:
>
> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing under suitable nutrient conditions, vertebrate cells comprising amplified *DNA encoding* the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycoslated erythropoietin polypeptide expressed by said cells.

Id. at col. 38: 50-59 (emphasis added) (paragraph structure altered).

3. Summary of the Parties' Arguments

HMR/TKT's proposed claim construction rests on the argument that the word "encoding" means "producing." HMR/TKT's Mem. in Opp'n re '698 [Doc. No. 700] at 8. HMR/TKT argues that the phrase at issue in Amgen's '698 patent means that the DNA actually produces a glycosylated erythropoietin polypeptide having a 166 amino acid sequence. *Id.* In other words, HMR/TKT argues that section (a) of claims 4 and 6 of the '698 patent should be construed to require the production of an EPO protein with 166 amino

acids. *Id.* at 1; HMR/TKT's Reply re '698 [Doc. No. 725] at 3.

Amgen agrees that the term "mature erythropoietin amino acid sequence of FIG 6" refers to a fully processed EPO glycoprotein having a 166 amino acid sequence. Amgen argues, however, that section (a) of the disputed claims refers to the *DNA* that encodes the fully processed EPO glycoprotein—not to the EPO glycoprotein itself. In other words, Amgen argues that the disputed claims refer to the type of DNA that is involved and describe that DNA as one that has a certain sequence, the genetic code, for the amino acid sequence spanning +1 through +166 of Figure 6. Amgen's Reply re '698 [Doc. No. 731] at 6. Amgen asserts that the proper construction of the claim language is "a DNA sequence that contains the genetic code for the amino acid sequence spanning from position +1 through position +166 of Figure 6." Amgen's Reply re '698 at 6. Amgen contends that a process can contain DNA that encodes the full 166 amino acids but result in an end-product that does not have the full 166 amino acid sequence. Thus, according to Amgen, this portion of the disputed claims refers to a *type* of DNA and to what that DNA *encodes*—not the end-protein that is ultimately *produced.*

4. Discussion

It is true that the Court construed the "mature erythropoietin amino acid sequence of FIG. 6," as stated in both the '080 and '698 patent, to mean a mature (fully realized) erythropoietin having 166 amino acids. *Amgen I*, 126 F. Supp. 2d at 100. HMR/TKT's argument that "DNA encoding . . .[the] amino acid sequence of FIG. 6" means that the DNA actually must produce an EPO with a 166 amino acid sequence, however, stretches this construction too far.

The Court notes that HMR/TKT supports its definition of "encoding" primarily with extrinsic evidence—evidence to

which resort ought be had only "if necessary." *Vitronics*, 90 F.3d at 1583. As will be discussed below, use of extrinsic evidence here is not appropriate in construing these terms because "the patent documents, taken as a whole," are sufficient "to enable the court to construe [the] disputed claim terms." *Id.* Moreover, even if it were necessary, and thus appropriate, for this Court to consider extrinsic evidence as to the meaning of the word "encoding," HMR/TKT's arguments would still fail. HMR/TKT misinterprets the extrinsic evidence to which it points from the first trial. Dr. Kingston did indeed state that "the protein that is encoded is the protein that is actually produced," Kingston Test., Trial Tr. at 1390-91, but this does not define "DNA encoding" as referring directly and exclusively to the specific product that is actually produced. Instead, what this language requires is DNA that is *capable* of encoding the final product—not DNA that produces the final product. HMR/TKT's interpretation of Dr. Lodish's testimony is also faulty. In the trial transcript pages to which HMR/TKT referred, Dr. Lodish never states that "encoding" means "producing," nor does Dr. Lodish define the fragment in question. He does indeed explain the end of the process as one that produces the same EPO glycoprotein. Lodish Test., Trial Tr. at 156-60. But this is the same point. Amgen's argument, and it is a sound one, is that this part of the claim is not describing the last step of the process, but an interim step—one that requires a DNA with a certain type of sequence or encoding capability.

Furthermore, the extrinsic evidence adduced during the second trial shows that "DNA encoding" in these claims does not mean that the end product must be produced. Dr. Lodish testified that those of skill in the art at the time would understand the plain meaning of the disputed term to mean "a DNA which when copied into RNA, and if necessary spliced, specifies the order of amino acids that are the mature erythropoietin amino-acid sequence depicted in Figure 6 of

the patent."[49] Lodish Test., R. Trial Tr. at 1054: 17-22, 1058: 10, 1059: 1-3 (explaining that genes have two parts, one of which involves the "coding sequence, the piece of DNA that actually specifies the amino acids in the encoded product" and stating that it is this part that is the subject of the claim, "that is, it is an issue of DNA encoding specifying an amino-acid sequence as determined by the genetic code"); *id.* at 1059: 16-21 (stating that "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" refers to "the DNA sequences that encode all of the amino acids from +1 to +166 of the EPO sequence"); *id.* at 1063: 17-19 (explaining that "DNA encoding" refers to DNA in the cell, not to "the polypeptide that is ultimately secreted by the cell. It's a statement of the coding capacity of the DNA in the cell"); *id.* at 1055: 13-18 ("It simply refers to a sequence of DNA which has the capability of encoding, which encodes, a particular protein. It is not a statement about a protein that the cell actually makes or secretes."). Indeed, even Dr. Kingston, HMR/TKT's expert, admitted that one way the word "encoding" "could be used very precisely is to describe a very, very precise small bit of the gene, and that is the codons." Kingston Test., R. Trial Tr. at 163: 2-16.[50] Further, consistent with Dr. Lodish's testimony, Dr. Kingston stated that the phrase "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" means "DNA that provides the instruction to make th[e] protein which would be the sequences" found in Figure 6 and depicted as the codons encoding amino acids +1 through +166. Kingston Test., R. Trial Tr. at 135: 2-142: 7 (circling the entire sequence

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[49] "RNA" is short for "ribonucleic acid."

[50] Dr. Kingston explained that the other "perfectly valid" way the word can be used, depending on the context, is to "describe all the instructions to make the mature protein." Kingston Test., R. Trial Tr. at 163: 7-12. In other words, Dr. Kingston testified that the term can also mean that it provides all the instructions necessary to allow a certain protein to be made.

of Figure 6); Lodish Test., R. Trial Tr. at 1059: 22-1060: 25 (same).

Again, however, none of this evidence is necessary to the Court's construction because an examination of the plain and ordinary meaning of the words, the claims themselves, and the specification demonstrates that HMR/TKT's asserted construction is off base. *Vitronics*, 90 F.3d at 1582; *SRI Int'l*, 775 F.2d at 1118; *Autogiro*, 384 F.2d at 397.[51]

a. The Plain and Ordinary Meaning

The plain and ordinary meaning of "encode" is to "convert from one system of communication to another" and "to convert (a message) into code." *Webster's Ninth New Collegiate Dictionary* 1990. This implies that "DNA encoding" is DNA that converts one type of message or text into another type of message and that it provides information to the cell.

b. The Claims

The claim language supports the plain and ordinary meaning of the term. The claim language establishes that "DNA encoding" refers to DNA that contains a certain sequence in the cells. Both claims 4 and 6 describe processes for producing a glycosylated erythropoietin polypeptide. The sentences in section (a) of the disputed claims do not, as HMR/TKT argues, require the production of the end-product of the claimed processes—an EPO polypeptide with 166 amino acids. To the contrary, the claims clearly distinguish between the cells grown in step (a) (which comprise "DNA encoding the mature erythropoietin amino acid sequence of Figure 6") and the EPO glycoprotein itself that is isolated in step (b). Here, the "mature erythropoietin amino acid sequence of FIG. 6" modifies "DNA encoding" in the cells grown in step (a)—not the "glycosylated erythropoietin

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[51] Neither party directed the Court to the prosecution history. Therefore, the Court will not look to it to construe the disputed term.

polypeptide" isolated in step (b). Therefore, based on the claim language and the ordinary meaning of the words, it appears that the sentences containing the disputed phrase mean, in conjunction, that the DNA must provide or contain the code or instructions for the "mature erythropoietin amino acid sequence of FIG. 6."

The claims do not, however, imply that a protein with the "mature erythropoietin amino acid sequence of FIG. 6" must at the end of the process be produced. This point becomes clear when comparing these claims to that of the '080 patent. The '698 claims recite a "DNA *encoding* the mature erythropoietin amino acid sequence of FIG. 6." as opposed to the claims of the '080 patent that specifically recite an *EPO glycoprotein* that "comprises the mature erythropoietin amino acid sequence of FIG. 6." '080 Patent, Ex. 1, col. 38: 42-43.

In a nutshell, HMR/TKT's construction conflates the concept of DNA that encodes for a protein with requiring the production of a specific protein and in so doing ignores how proteins are actually produced. The DNA encodes the protein. It provides the instruction set used by the *cell* to synthesize a polypeptide that is later processed to its final form. DNA encoding a specific amino acid sequence, however, does not necessarily determine the final length of the polypeptide produced by the cell. The testimony adduced at trial regarding the 166th arginine makes this clear. Dr. Lodish explained that "as long as that DNA encodes the mature erythropoietin—mature EPO sequence, it matters not at all how many other amino acids might be there. Whatever it is, as long as it encodes that sequence, it's fine." Lodish Test., Trial Tr. at 248: 23-249: 1.

HMR/TKT counterargues that it is the protein that is produced by the cell that determines what instructions were actually present in the cell *and used* in the process, that is, that erroneous instructions are not really instructions at all. *See, e.g.*, 7/28/03 Hr'g Tr. at 52: 1-9 (explaining that "there's no proof one way or another as to what the intermediary

is," and "the only proof that there is in this case is as to the end product").[52]

The Court, however, is not persuaded. The evidence adduced at the first trial overwhelmingly suggested that although the DNA encodes for a 166 amino acid sequence, ultimately, the *cell* cleaves off the last amino acid residue prior to secretion of the final protein, EPO that has a 165 amino acid sequence. *Amgen I*, 126 F. Supp. 2d at 86, 101; Lodish Test., Trial Tr. at 347: 16- 18, 348: 3-9; 7/28/03 Hr'g Tr. at 52: 1-9. As Amgen's counsel explained at the *Markman* hearing, "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" is DNA containing codons for amino acids 1-166 of FIG. 6. These instructions will be used by the cell to produce a 165 amino acid erythropoietin. 7/28/03 Hr'g Tr. at 44: 11-47: 11.[53] Thus, DNA can encode or

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[52] HMR/TKT believes it somehow bolsters its argument by pointing out that the Court construed the word "mature" to mean the "*fully realized* form of the amino acid sequence of Figure 6," *Amgen I*, 126 F. Supp. 2d at 87 (emphasis). This argument, however, fails to persuade the Court, for it does not change the definition of DNA encoding, it merely refines what is being encoded.

[53] Amgen's counsel provided a brief, undisputed, refresher for the Court as follows:

> [T]he DNA encodes EPO. The DNA is transcribed to make a messenger RNA. That messenger RNA is then reprocessed in the cell. That messenger RNA is extruded from the nucleus. A ribosome binds to it, translates the messenger RNA into a protein. And a protein that is a copy of the entire DNA sequence of the messenger RNA, including both the leader sequence and the . . . amino acid position 166, is made in the cell. The cell then . . . further processes that protein cutting off . . . the leader sequence of the protein and the amino acid at 166, and that is done before the cell then secretes the fully processed form of the hormone. . . . And as the protein is secreted from the cell, even though it's encoded by DNA that has 166 amino acid, the cell actually produces a protein that has 165 amino acid.

7/28/03 Hr'g Tr. at 45: 21-46: 12.

provide the genetic instructions for a protein that when ultimately secreted has a structure different from the one that the instructions dictate. That some of these instructions are not in the end "used" does not erase the fact that the DNA contained the information in the first place.

Moreover, as Amgen argues, HMR/TKT's construction makes the claims illogical. With HMR/TKT's construction, the claimed processes would require the use of a cell containing "a promoter DNA operatively linked to an EPO protein" or "an amplified EPO protein." Amgen's Mem. In Opp'n re '698 [Doc. No. 717] at 6-7. As asserted by Amgen and undisputed by HMR/TKT, this does not make sense.

In sum, any argument based on the claims that the words "producing" or "that produces" should be inserted in lieu of "encoding" fails along with HMR/TKT's argument that "encoding" refers to the EPO protein itself.[54]

c. The Specification

Like the claims, the specification supports the plain and ordinary meaning of the word "DNA encoding." It demonstrates that one skilled in the art at the time would have defined "encoding" as providing genetic instructions, that is, the sequence.

At the *Markman* hearing, HMR/TKT pointed to columns 11 and 13 in the specification to support its argument that DNA encoding means producing or that the protein is

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[54] It is true that the Court construed the term "mature erythropoietin amino acid sequence of FIG. 6" in the '080 patent to refer to the structure of the claimed EPO glycoprotein. In the '698 patent, however, the claims refer to the structure of the DNA, not of a protein.

actually produced. 7/28/03 Hr'g Tr. at 51: 6-11. Those sections state that:

> The isolation of the desired cDNA clones containing EPO encoding DNA was accomplished through the use of DNA/DNA colony hybridization.

'933 Patent, Ex. 1, col. 13: 64-66.

> Specifically comprehended in part (b) are genomic DNA sequences encoding allelic variant forms of monkey and human erythropoietin and/or encoding other mammalian species of erythropoietin. Specifically comprehended by part (c) are manufactured DNA sequences encoding EPO, EPO fragments and EPO analogs which DNA sequences may incorporate codons facilitating translation of messenger RNA in non-vertebrate hosts.

'933 Patent, Ex. 1, col. 11: 54-61.

As this Court pointed out during the hearing, however, neither of these sections equates "encoding" with producing. 7/28/03 Hr'g Tr. at 51: 12-15. Likewise, neither shows a clear and deliberate attempt by the patentee to become its own lexicographer. *See Renishaw*, 158 F.3d at 1249; *Vitronics*, 90 F.3d at 1582; *Altiris*, 318 F.3d at 1370; *Teleflex*, 299 F.3d at 1326. Each can be read consistently with the ordinary and customary meaning as understood by one skilled in the art, that is, inserting "providing the genetic instructions for" in lieu of "encoding." In fact, the section to which HMR/TKT points in column 11 works against its argument that "DNA encoding" means DNA producing the actual protein because it refers to DNA sequences encoding EPO and EPO fragments. Under HMR/TKT's construction, this section would require EPO fragments actually to be produced instead of requiring that the DNA have the genetic instructions for, that is, provide the codons or genetic sequence for, EPO fragments.

5. Conclusion and Claim Construction of "DNA Encoding"

Accordingly, the Court construed "DNA encoding" to mean "the genetic instructions for." 7/28/03 Hr'g Tr. at 56: 18-23.[55] TKT/HMR, however, did not give up. As a last-ditch effort to win on literal infringement—which is what claim construction is really all about—HMR/TKT argued at the second trial via Dr. Kingston's testimony that "genetic instructions for," the Court's construction of DNA encoding, could mean either the codons for the amino acids plus 1 to 166 of Figure 6 of the patent, or alternatively, all the instructions to make the mature protein including the regulatory sequences. Kingston, R. Trial Tr. at 161-163. Dr. Kingston explained that a scientist could use the term differently depending on the context. *Id.* To be clear, in this context, the Court interprets the claim to be referring to the coding sequence, the piece of DNA that actually specifies the amino acid sequence—not the regulatory sequences that determine when and under what conditions the cells copy the gene into RNA.[56] This interpretation is supported by the claims themselves, which refer to DNA that encodes—provides the genetic instructions for—"the mature erythropoietin amino acid sequence of FIG. 6." Figure 6 indeed depicts, among

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[55] The Court noted that this construction applied any time DNA encoding was used throughout the various claims. 7/28/03 Hr'g Tr. at 56: 18-23.

[56] Dr. Lodish and Dr. Kingston appear to agree that there are two parts to genes. "One is the regulatory sequences that determine when and under what conditions the cells copy the gene into RNA; and the second is the coding sequence, the piece of DNA that actually specifies the amino acids in the encoded product." Lodish Test., R. Trial Tr. at 1058: 20-25. They disagree about to what this claim is referring. Interestingly, at the same time that Dr. Kingston claims that this Court's construction means the regulatory sequences—all the instructions for the protein—he admits that "[t]he DNA that encodes each amino acid is the same" in both Amgen's and HMR/TKT's cells. Kingston Test., R. Trial Tr. at 162: 18-19.

other things, the deduced amino acid sequence that is arrived at by reading the codons of the DNA encoding the protein. Importantly, HMR/TKT points to no support in the prosecution history for its argument on this point. Thus, the Court interprets the claims to require the use of cells containing DNA that provides the genetic instructions, the codons, for a 166 amino acid sequence.

C. Are Claims 4 and 6 of the '698 Patent Step-Plus-Function Claims?

1. Background[57] and Summary of The Parties' Arguments

Whether Amgen, in referring to the "step[] of . . . growing under suitable nutrient conditions" in claims 4 and 6 of the '698 patent, was making step-plus-function claims is an issue raised for the first time by HMR/TKT in its Memorandum in Opposition to Amgen's Renewed Motion for Summary Judgment of infringement of claims 4-9 of the '698 patent. HMR/TKT's Mem. In Opp'n re '698 [Doc. No. 700] at 9. Paragraph 6 of 35 U.S.C. § 112, which sets forth the notion of step-plus-function and means-plus-function, "obligates this court to interpret each functional element in a combination claim by reference to the corresponding structure, material, or acts described in the *specification and their equivalents*." *Seal-Flex, Inc.* v. *Athletic Track and Court Const.*, 172 F.3d 836, 843 (Fed. Cir. 1999) (emphasis added); *O.I. Corp.* v. *Tekmar Co., Inc.*, 115 F.3d 1576, 1583 (Fed. Cir. 1997).[58] In

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[57] For more background, see background discussion regarding construction of the term "DNA encoding."

[58] The purpose of section 112, paragraph 6 was

> to permit use of means expressions without recitation of all the possible means that might be used in a claimed apparatus. . . . The price that must be paid for use of that convenience is limitation of the claim to the means specified in the written description and equivalents thereof. Similarly, a step for accomplishing a particular function in a process claim may also be claimed without specificity subject to the same price.

O.I. Corp., 115 F.3d at 1583 (internal citations omitted).

other words, if this section applies, the Court must limit its infringement analysis to a comparison of the type of "growing" claimed in the *specification* to the type of growing utilized by HMR/TKT.

Ironically, this is exactly what the Court did—*in error*—in the first go-round. In *Amgen I*, the Court based its holding of non-infringement of the '698 patent on a comparison of HMR/TKT's process to the processes outlined in the patent specification.[59] This was error because the Court had never ruled that the relevant claims qualified as a step-plus-function claims.[60] HMR/TKT now presses the Court to address the issue and so to rule.

The wrinkle here is whether the Court now can address this issue—that is, whether the Court can or should permit HMR/TKT to raise the argument at this stage. After all, in 2000, the Court issued a sanction order against HMR/TKT limiting it to the contentions specifically described in its responses to interrogatories. Amgen's Mem. in Opp'n re '698 & '349 [Doc. No. 717] at 4; Amgen's App. to Mem. in Opp'n re '698 & '349 [Doc. No. 719], Ex. A (1/28/00 Order Granting Sanction). HMR/TKT never identified its step-plus-

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[59] The Court compared the accused process to the preferred embodiment in the claim and concluded that "HMR/TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification" because it "utilizes the endogenous rather than exogenous EPO gene" and it "places it promoter upstream from rather than adjacent to the EPO gene." *Amgen I*, 126 F. Supp. 2d at 122.

[60] In other words, the Court went straight to a step-plus-function approach without first ruling that these were indeed step-plus-function claims. As will be discussed *infra*, the Court mentioned to the parties when giving a ruling of non-infringement of the '698 patent, that it was considering a means-plus-function type of analogy. When writing the opinion, however, the Court did not address whether step-plus-function claims were indeed involved and, despite any discussions to the contrary, did not base its ruling of non-infringement of the '698 patent on a finding that it involved step-plus-function claims.

function theory in its responses to Amgen's contention interrogatories as a basis for non-infringement of the '698 patent. Amgen's App. to Mem. in Opp'n re '698 & '349, Tab C (12/7/99 HMR/TKT's Supplemental Answers and Objections to Amgen's Interrog. Nos. 2, 3, and 9) at 5-7, 17. Moreover, HMR/TKT never stated that this aspect of the '698 patent (i.e., whether it included a step-plus-function claim) needed to be resolved through a *Markman* hearing. Amgen asserts that the Court should therefore not allow this argument, and, at a minimum, the Court should afford Amgen the opportunity to present evidence directed to this new step-plus-function argument. *Id.* at 4-5. Moreover, Amgen argues that even if the Court allows such an argument, it lacks merit because "growing" is an "act," not a "function."

2. Discussion[61]

a. Should the Court Allow HMR/TKT to Make Its Step-Plus-Function Argument?

Whether the language of a claim is in step-plus-function format is a question of claim construction. *See, e.g., Kemco Sales, Inc.* v. *Control Papers Co., Inc.*, 208 F.3d 1352, 1360 (Fed. Cir. 2000) ("Whether the language of a claim is to be interpreted according to 35 U.S.C. § 112, ¶ 6, i.e., whether a claim limitation is in means-plus-function [or step-plus function] format, is a matter of claim construction and is thus a question of law, reviewed de novo."); *Personalized Media Communications, LLC* v. *Int'l Trade Comm'n*, 161 F.3d 696, 702 (Fed Cir. 1998) ("An infringement analysis entails two steps. . . . The first step, claim construction, is a question of law which we review de novo. . . . The second step is factual. . . . Whether certain claim language invokes 35 U.S.C. § 112, ¶ 6 is an exercise in claim construction and is therefore a question of law." (citations and internal quotation

[61] See the preceding section regarding "DNA encoding" for recitation of claims 4 and 6 of the '698 patent.

marks omitted)). Generally, on appeal, a party cannot proffer a new claim construction that changes its scope, but it can present additional arguments in support of a previously proposed construction. *See, e.g.*, *CCS Fitness, Inc.* v. *Brunswick Corp.*, 288 F.3d 1359, 1371 (Fed. Cir. 2002). The rationale is that the parties deserve notice and an opportunity to develop the record and, at the same time, the appellate court needs to have a properly reviewable record on an issue raised on appeal. *Interactive Gift Exp., Inc.* v. *Compuserve, Inc.*, 256 F.3d 1323, 1346-46 (Fed. Cir. 2001); *cf. Finnigan Corp.* v. *Int'l Trade Comm'n*, 180 F.3d 1354, 1363 (Fed. Cir. 1999). Thus, a relevant inquiry in determining whether a new claim construction can be pressed is "whether the trial court and the party claiming waiver had fair notice and an opportunity to address the issue concerning the scope of a claim limitation." *CCS Fitness*, 288 F.3d at 1371.

The situation here is unusual. First, this is not a new claim construction argument raised on appeal but instead a new claim construction argument raised on remand to the trial court. Second, counsel for Amgen—the party now seeking to have the issue deemed waived—acknowledged the possible applicability of the step-plus-function doctrine to the Court. On June 9, 2000, after the Court made its finding of non-infringement of the '698 patent, Amgen queried whether the Court was construing the '698 process claims as "means plus function" claims. Trial Tr. at 1308-1309. The Court replied as follows:

> I don't mean to be elliptical. That is my analogy. That's right. . . . Now I think you've missed on the '698 patent. I think that because I do think you have to spell out a means-plus-function. And I have read this patent with great care and I've reflected on it throughout the

> testimony of all the witnesses. I don't see either by equivalent or by literal infringement.

Trial Tr. at 1309-1310. Thus, the Court referred to the means-plus-function doctrine in relation to the '698 patent[62] but, as noted earlier, did not definitively rule that the asserted claims were in means or step-plus-function format nor even mention stepplus-function in the opinion despite applying the infringement analysis required when a claim is in step-plus-function format.

Although the situation is not straightforward, it is clear that Amgen was on notice of the issue but did not get an opportunity to argue it. Given the procedural posture of the case with respect to the '698 patent specifically, Amgen was fully afforded the opportunity during the remand trial to address the issue, which substantially reduces any prejudice to it.

Indeed, the Federal Circuit has suggested that it is appropriate to consider whether a claim is in means-plus-function or step-plus-function format even when one party has essentially waived the issue. *Rodime PLC* v. *Seagate Technology, Inc.*, 174 F.3d 1294 (Fed. Cir. 1999). In that case, the parties contested at trial whether the plaintiff's claim was in means-plus-function format, with the plaintiff arguing that it was not. *Id.* at 1302. The district court ruled that the claim was in means-plusfunction format. *Id.* The plaintiff appealed, but did

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[62] The fact that Amgen's counsel and the Court referred to "means-plus-function" as opposed to "step-plus-function" makes little difference in the Court's analysis here because the two concepts are very closely related, enough so that mention of one provides notice of the potential that the other may apply. *Seal-Flex*, 172 F.3d at 848 (noting that although they require distinct analyses, they are similar and that 35 U.S.C. § 112 ¶ 6 suggests a strong correlation between the two); *see also O.I. Corp.*, 115 F.3d at 1583. To that end, the Federal Circuit has suggested using means-plus-function case law to "give guidance for determining whether a claim element is in step-plus-function form so as to invoke the statute's claim interpretation requirements." *Seal-Flex*, 172 F.3d at 848.

not press that particular issue and thus apparently conceded that the claim was in means-plus function format. *Id.* The Federal Circuit nonetheless assessed *de novo* whether the claim was indeed in means-plus-function format, explaining that:

> [The plaintiff's] concession . . . does not relieve this court of its responsibility to interpret the claims as a matter of law. To interpret the claims, this court must decide the subsidiary question of whether the claim element disputed by the parties invokes § 112, ¶ 6 in the first instance. . . . Only by undertaking this inquiry can this court ensure consistency in statutory application. Moreover, this court's claim interpretation affects entities beyond the parties to this case. Therefore, this court examines the district court's decision that this claim falls under § 112, ¶ 6.

Id. (internal citations omitted). The Federal Circuit subsequently concluded that the district court had erred and that the claim was not in means-plus-function format.

Similarly, in this case, whether this portion of the '698 patent is in step-plus-function format determines the entire analytic framework for analyzing whether HMR/TKT's process infringes this part of the patent. To make this assessment, therefore, this Court needs to determine which analytic framework is implicated. The Court can either make this decision on the merits or can simply decide that the regular infringement framework must be used because HMR/TKT waived its argument that the step-plus-function framework should be used. The problem with the latter approach is that, if the step-plus function framework is truly the applicable one, and the Court nonetheless declines to use it on grounds of waiver, the Court will essentially be applying the wrong law to this aspect of the claim. This, in turn, undermines consistency in statutory application.

For these prudential reasons, this Court analyses whether claims 4 and 6 of the patent are step-plus-function claims. It does so in the course of construing the claims because, as noted above, whether the language of a claim is in step-plus-function format is a question of claim construction. *See, e.g., Kemco Sales, Inc.*, 208 F.3d at 1360; *Personalized Media Communications, LLC*, 161 F.3d at 702.

b. Are Claims 4 and 6 of the '698 Patent Step-Plus-Function Claims?

This is a close question, but, on balance, claims 4 and 6 of the '698 patent do not qualify as step-plus-function claims.[63] Five reasons support this conclusion.

First—although this is not dispositive—the words "steps of" are used in the claim. Such a grammatical structure indicates that this is not a step-plus-function claim, because the phrase "steps of" colloquially signals the introduction of specific acts, rather than functions. *See Seal-Flex*, 172 F.3d at 850 ("[T]he . . . phrase 'steps of' tend[s] to show that § 112, ¶ 6 does not govern that limitation. Accordingly, this court has similarly denied step-plus-function treatment to method claims which use the conventional 'steps of' language."); *see also O.I. Corp.*, 115 F.3d at 1582-83; *Serrano* v. *Telular Corp.*, 111 F.3d 1578, 1583 (Fed. Cir. 1997). Similarly, Amgen did not use the phrase that typically signals the introduction of a step-plusfunction limitation: "step for." *See Seal-Flex*, 173 F.3d at 849 (Rader, J., concurring); *Masco Corp.* v. *United States*, 303 F.3d 1316, 1326-27 (Fed. Cir. 2002). Accordingly, there is a presumption that section 112, paragraph 6 does not apply, that is, that this is not a step-plus-function claim. *Generation II Orthotics Inc.* v. *Med. Tech. Inc.*, 263 F.3d 1356, 1368 (Fed. Cir. 2001).

Second, upon examination, the claim element "growing" appears to recite a specific act for performing an ultimate

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[63] Thus definitive resolution of the procedural dispute is unnecessary.

function, that is, it appears to explain how the function is accomplished, rather than reciting the ultimate function itself. This is a key distinction. As Judge Rader explained in his concurrence in *Seal-Flex*, "the 'underlying function' of a method claim element corresponds to *what* that element ultimately accomplishes in relationship to what the other elements of the claim and the claim as a whole accomplish. 'Acts,' on the other hand, correspond to how the function is accomplished." *Seal-Flex*, 172 F.3d at 849-50. Here the "what" that is ultimately accomplished is the production of glycosylated erythropoietin, and the "how" is "growing [vertebrate cells] under suitable conditions."[64] The dictionary definition of "growing" supports the interpretation that this is an act. *Masco*, 303 F.3d at 1327 (looking to a mechanical

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[64] Expert testimony by one skilled in the art—extrinsic evidence which the Court need not to resort—implicitly supports defining "growing" as an act. Dr. Tlsty made clear that the term "growing" was one that was easily understood by one skilled in the art when he stated, without explanation, that he has "been growing and culturing cells since [he] was an undergraduate." Tlsty Test., Trial Tr. at 832: 11-16; *cf. Greenberg* v. *Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1582 (Fed. Cir. 1996) (stating in the means-plus-function context that "[w]hat is important is . . . that the term, . . . has a reasonably well understood meaning in the art"); *see also Watts* v. *XL Sys., Inc.*, 232 F.3d 877, 881 (Fed. Cir. 2000); *Caterpillar Inc.* v. *Detroit Diesel Corp.*, 961 F. Supp. 1249, 1256 (N.D. Ind. 1996) (quoting *Greenberg*, 91 F.3d at 1583 ("The acts set forth in Claim 1's elements are 'functional' only in the manner in which all acts are functional, and nothing before the court suggests that the acts set forth in the claim lack a 'reasonably well understood meaning in the art.'").

The way in which HMR/TKT described the culturing and growing of its cells in Investigational New Drug Application ("IND") for HMR 4396 provides further evidence that the term has a reasonably well-understood meaning in the art. For example, it stated that "[C]ells grown as attached cultures in static flask were released by trypsination. The cells were resuspended in LONZA Biologics proprietary HM9 Serum-free medium . . . . Once a reliable pattern of growth was established, the serum supplement was progressively eliminated from the medium." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab T (Ex. 19, IND for HMR 4396) at 574.

engineering dictionary and a regular unabridged dictionary to determine whether "transmitting" is an act); *Vitronics*, 90 F.3d at 1584 (noting that judges are free to consult technical treatises and dictionaries "so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents"). Here, the dictionary definitions of growing are "to increase in size by a natural process" or "to develop and reach maturity." The *American Heritage Dictionary, supra*, at 579. These definitions support that growing is an act. Moreover, they do not contradict the meaning of "growing" that may be inferred from the prosecution history, and HMR/TKT does not argue that Amgen defined the term to have anything other than its plain and customary meaning.

Third, HMR/TKT does not even attempt to explain, much less show, how Amgen's language—"growing under suitable nutrient conditions"—fails to describe an act. "[W]here a method claim does not contain the term 'step[s] for,' a limitation of that claim cannot be construed as a step-plus-function limitation *without* a showing that the limitation contains no act." *Masco*, 303 F.3d at 1327 (emphasis added). To the contrary, HMR/TKT makes only a half-hearted assertion—in a footnote in a memorandum in opposition—that these claims are in step-plus-function format. Indeed, the footnote merely states that the argument HMR/TKT made with reference to claim 7 of the '349 patent can be applied to claims 4 and 6 of the '698 patent. HMR/TKT's Mem. In Opp'n re '698 at 9 n.**.[65] HMR/TKT does not dispute Amgen's evidence, but simply claims that "growing" is not an act. HMR/TKT contradicts itself, however, as it implicitly refers to "growing" as an act in the Corrected Joint Pretrial Memorandum when it admits that HMR 4396 is produced by "growing, under suit-

[65] As will be discussed, HMR/TKT made a more detailed argument that claim 7 of the '349 patent is a step-plus-function claim. This argument fails, however, so it also fails when applied to the '698 patent.

able nutrient conditions R223 cells." Amgen's App. to Mot. for Judgment re '349 [Doc. No. 676], Tab M (4/26/00 Corrected Joint Pretrial Mem.) ¶ 25. This implies that "growing . . ." is not in step-plus-function format. If "growing" was a function and needed further explanation, arguably HMR/TKT would not have admitted to such a statement in the Joint Pretrial Memorandum—at least not without further explanation. HMR/TKT cannot merely assert that there is "no act" contained in this part of the claim without producing some evidence that there is not, i.e., that growing is not an act. *Celotex Corp.* v. *Catrett*, 477 U.S. 317, 324 (1986) (quoting Fed. R. Civ. P. 56(e)) (stating that the non-moving party must "go beyond the pleadings, and by [its] own affidavits, or by the 'depositions, answers to interrogatories, and admissions on file,' designate 'specific facts showing there is a material issue for trial'"); *Seal-Flex*, 172 F.3d at 849-50 (noting that step-plus-function applies only when the "limitation contains nothing that can be construed as an act").

Fourth, the Federal Circuit has made clear that "claiming a step by itself, or even a series of steps, does not implicate section 112, ¶ 6," and that courts must be

> careful not to extend the language of this provision to situations not contemplated by Congress. If we were to construe every process claim containing steps described by an "ing" verb, such as passing, heating, reacting, transferring, etc. into a step-plus-function limitation, we would be limiting process claims in a manner never intended by Congress.

O.I. Corp., 115 F.3d at 1583. If the Court were to construe this process claim that begins with "growing"—an "ing" verb very much like heating, reacting, or transferring—as a step-plus-function limitation, it would be doing just that, that is, limiting the process claims in a manner never intended by Congress. Moreover, the Court would be "render[ing] the scope of coverage of these method claims uncertain and

disrupt[ing] the patentees' settled expectations regarding the scope of their claims." *Masco*, 303 F.3d at 1327 (noting that "method claims are commonly drafted . . . by reciting the phrase 'steps of' followed by a list of actions comprising the method claimed").

As a final matter, the Federal Circuit's silence as to whether these claims are step-plus-function claims may be indicative. True, the Federal Circuit probably may not even have considered the possibility.[66] Alternatively, however, the Federal Circuit may have considered the step-plus-function possibility but rejected it as without merit. This latter interpretation of the Federal Court's silence is supported by the Federal Circuit's statement that this Court's analysis (comparing HMR/TKT's process to the specification) was "legally unsupportable." *Amgen II*, 314 F.3d at 1350-51. If the analysis was "legally supportable" by, for example, a finding that the claim was in step-plus-function format, the Federal Circuit certainly could have reached in and decided the issue itself, *see Rodime*, 174 F.3d at 1294. While it is true that in *Rodime*, the issue had been squarely before the district court and thus apparent to the Federal Circuit, here the issue was flagged by the way this Court erroneously conducted its infringement analysis. To anyone familiar with patent law, step-plus-function would have come to mind upon reading the Court's infringement analysis which limited Amgen's processes to those outlined in the specification. That the Federal Circuit failed to address the issue may, therefore, be significant. *Ethicon Endo-Surgery, Inc.* v. *U.S. Surgical Corp.*, 93 F.3d 1572, 1582 (Fed. Cir. 1996) ("We must affirm the decision of the district court if it is supported by any ground properly preserved on appeal."); *Datascope Corp.* v. *SMEC Inc.*, 879 F.2d 820, 822 n.1 (Fed. Cir. 1989) ("Appellees

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[66] The issue was likely never brought to the Federal Circuit's attention since neither party, on appeal, had anything to gain in bringing it up.

always have the right to assert alternative grounds for affirming the judgment that are supported by the record.").

3. Conclusion and Claim Construction

Though it is a close question, this Court rules that claims 4 and 6 of the '698 patent, in referring to the "steps of: (a) *growing under suitable nutrient conditions . . .*," are not step-plus-function claims and that the regular infringement framework should therefore apply.

D. Is Claim 7 of the '349 Patent a Step-Plus-Function Claim?

1. Background

Amgen's '349 patent contains six product claims (claims 1-6) and one process claim (claim 7). '349 Patent, Ex. 1. This Court held, and the Federal Circuit affirmed, that HMR/TKT's HMR 4396 literally infringes the product claims of the '349 patent. *Amgen II*, 314 F.3d at 1352, 1358. Based on a comparison between the accused product and the preferred embodiment, this Court held that HMR/TKT did not literally or equivalently infringe the process claim, claim 7. *Amgen I*, 126 F. Supp. 2d at 122. The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this ruling and remanded it so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1351, 1347, 1313. Therefore, the remaining issue regarding this patent is whether HMR/TKT's HMR 4396 infringes claim 7.

2. The Claim at Issue

Claim 7 of the '349 Patent:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.

'349 Patent, Ex. 1, col. 38: 34-36.

3. Summary of the Parties' Arguments

HMR/TKT, in an effort to establish non-infringement of claim 7, has argued, as it did with claims 4 and 6 of the '698 patent, that claim 7 is a step-plus-function claim and that 35 U.S.C. § 112, ¶ 6 therefore applies. As such, it contends that its product does not literally infringe the "step of culturing" because HMR/TKT's process does not involve the culturing procedures set forth in Amgen's specification. HMR/TKT's Mem. In Supp. [Doc. No. 687] at 12-13. As with the '698 patent, Amgen argues, as a preliminary matter, that HMR/TKT is improperly basing its motion under Fed. R. Civ. P. 52(c) on new arguments and defenses, given the previous orders of this Court and Amgen's lack of opportunity to address these issues. Amgen's Mem. In Opp'n re '698 & '349 [Doc. No. 717] at 3-5. Furthermore, Amgen points out, the procedural context here is different than it was with the '698 patent, as this Court heard the entirety of both parties' arguments and evidence concerning '349 claims 1, 3, 4, 6, and 7. Lastly, Amgen argues, for the same reasons that it did regarding the '698 patent, that claim 7 is not a step-plus-function claim. *Id.* at 11-14.

4. Discussion

a. Should the Court Allow HMR/TKT to Make Its Step-Plus-Function Argument?

Here, there is the same wrinkle that there was with the step-plus-function argument respecting the '698 patent: should the Court permit HMR/TKT to raise this argument at this late stage in the game? There are two differences, however, that make the wrinkle, in the context of this patent, harder to iron out. First, the Court did not remark on the record, as it did with the '698 patent, that it was making a means-plus-function analogy in ruling on the '349 patent claims. Second, HMR/TKT has already presented its case of non-infringement regarding all the claims of the '349 patent.

Neither of these differences, however, prevents the Court from allowing HMR/TKT to make this argument at this point. The fact that the Court did not make a means-plus analogy to this patent is easily overcome since the Court, in *Amgen I*, explained that it found non-infringement of claim 7 of the '349 patent for the same reasons as it did the '698 patent. Thus, the parties were on notice that any analysis regarding the process claims of the '698 patent would necessarily apply to the '349 patent. The procedural landscape ought not prevent the Court from construing whether this is a step-plus-function claim. If it is such a claim, the Court ought not conduct its infringement analysis as though it were not. This claim is here on remand and the Court must construe it in accordance with the law. Thus, the Court reaches the same conclusion as it did with the '698 patent, that is, that it can and should address HMR/TKT's step-plus-function argument.

b. Is Claim 7 of the '349 Patent a Step-Plus-Function Claim?

The determination of whether claim 7 of the '349 patent is a step-plus-function claim must be made in the same way as any other determination regarding claim construction. As such, the Court must principally rely on intrinsic evidence and refer to extrinsic evidence only if necessary, with the exception that a dictionary or treatise—which qualifies as extrinsic evidence—can be consulted freely as long as it does not contradict the patent language.

The Court's assessment of whether "culturing" is a function rather than an act, such that the step-plus-function framework applies, tracks the analysis provided above with respect to the whether "growing" is a function rather than an act in the '698 patent. Just as the Court ruled that growing is an act, it rules that culturing is an act, and claim 7, therefore, does not state a step-plus-function limitation.

Like the asserted claims of the '698 patent, claim 7 contains the phrase "step of," rather than the phrase "step for." Accordingly, there is a presumption that section 112, paragraph 6 does not apply—that this is not a step-plus-function. *Generation II Orthotics Inc.*, 263 F.3d at 1368; *Seal-Flex*, 173 F. 3d at 849 (Rader, J., concurring); *Masco*, 303 F.3d at 1326-27.

HMR/TKT argues that "culturing" is the claimed function of claim 7. HMR/TKT's Mem. in Supp. re '698 & '349 [Doc. No. 687] at 13. Specifically, it claims that the "what" is "culturing." In other words, HMR/TKT argues that "culturing" is "what" the claim ultimately accomplishes, and nothing else in the claim describes "how" the culturing is accomplished. HMR/TKT's Reply Mem. re '698 & '349 [Doc. No. 725] at 9. While at first blush this argument makes sense, the Federal Circuit, in *Masco*, interpreted Judge Rader's formulation as requiring analysis of "what th[e] limitations ultimately accomplish in relation to what the other limitations and each claim as a whole accomplish." *Masco*, 303 F.3d 1316. Although there are no words in claim 7 that state the function, as Judge Rader explained in *Seal-Flex*, "the function of that element may nonetheless be discernible from the context of the overall claim and the disclosure in the specification." *Seal-Flex*, 172 F.3d at 850. Here, the claim states in its preamble that it is "a process for producing erythropoietin" suggesting that there is a larger, ultimate function and that "culturing" is merely one act that achieves it. While the "recitation of the overall function of the claim in the preamble does not suffice to convert each element into an act for performing that function so as to preclude application of section 112, paragraph 6," *Seal-Flex*, 172 F.3d at 850,[67] language

[67] Importantly, however, neither is the converse true: the Federal Circuit in *O.I. Corp.*, which dealt with a claim very similar to the claim here, held that "a statement in a preamble of a result that necessarily

in other claims of the patent lends further support to the Court's conclusion that "culturing" is an act. Here, claim 7 itself refers to, *inter alia*, product claims 1 and 4. Claims 1 and 4 describe the purpose of culturing vertebrate cells as being able to produce erythropoietin at a certain rate:

> *Claim 1:* Vertebrate cells which can be propagated in vitro and *which are capable* upon growth in culture *of producing erythropoietin* in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours . . .
>
> *Claim 4:* Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences . . . *for production of human erythropoietin*, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10^6 cells in 48 hours . . .

'349 Patent, Ex. 1, col. 38: 8-14, 21-27 (emphasis added). Hence, when considering what the "other limitations and each claim as a whole accomplish," it appears that "culturing" is not the claimed function but instead a single step or act of a process claim that "*ultimately accomplishes*" the production of erythropoietin at a certain rate. *Masco*, 303 F.3d at 1327 (emphasis added).

There are two other pieces of support for construing "culturing" as an act. First, both parties agreed that the claim term "culturing under suitable conditions" means "growing in vitro under appropriate [or suitable] conditions." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab P (9/20/99 App. to Amgen's Claim Construction Submission) at 7; *id.*, Tab Q (10/18/99 App. to HMR/TKT's Claim Construction Submission) at 5. Thus, implicitly HMR/TKT admitted that "cultur-

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follows from performing a series of steps does not convert each of those steps into step-plus-function clauses." *O.I. Corp.*, 115 F.3d at 1584.

ing" and "growing" are essentially interchangeable terms. This, considered in combination with the Joint Pretrial Memorandum itself, which states that HMR/TKT's HMR 4396 is produced by "growing, under suitable nutrient conditions R223 cells," 4/26/00 Corrected Joint Pretrial Mem. at 5, ¶ 25, suggests that even HMR/TKT at one point did not believe that "growing"—and by extension, "culturing"—was a function that needed further explanation. This strongly suggests that the term "culturing" was one reasonably well understood by those skilled in the art, a relevant consideration in determining whether a term is an act. *Cf. Greenberg* v. *Ethicon Endo-Surgery, Inc.*, 91 F.3d 1580, 1582 (Fed. Cir. 1996); *see also Watts*, 232 F.3d at 881; *Caterpillar*, 961 F. Supp. at 1256.[68]

Second, dictionary definitions of "culturing" define this word as an act. A standard medical dictionary, *Dorland's Medical Dictionary*, defines "culture" as "propagation of . . . living tissue cells in special media conducive to their growth." Amgen's App. to Mem. in Opp'n re '698 & '349, Tab R (*Dorland's Illustrated Med. Dictionary* (27th ed. 1988)), at 334; *see, e.g., Masco*, 303 F.3d at 1328 (relying on a standard mechanical engineering dictionary definition of "transmitting" to help determine whether it is an act). The *American Heritage Dictionary* describes the verb culturing to mean "to cultivate" or "to develop (microorganisms or tissues, for example) in a culture medium." *The American Heritage Dictionary, supra*, at 348; *see, e.g., Masco*, 303 F.3d at 1328 (relying on standard unabridged dictionary definition of "transmitting" to help determine whether it is an act); *Vitronics*, 90 F.3d at 1584. None of these definitions contradicts what is described in the patent.

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[68] As discussed earlier, expert testimony by Dr. Tlsty and assertions in the IND by HMR/TKT—extrinsic evidence to which the Court need not resort—also support that the terms "growing" and "culturing" have meanings reasonably well understood by those skilled in the art.

In sum, HMR/TKT has failed to show that the "limitation contains nothing that can be construed as an act." *Seal-Flex*, 172 F.3d at 850. On the contrary, "culturing"—that is, developing cells in a certain medium—can logically be construed as an act because it describes *how* the EPO is produced (i.e., by culturing the cells), and because "culturing" is itself a term well understood by those skilled in the art.

As a final matter, the Court notes the same concerns it had with construing "growing" as a step-plus-function limitation. If the Court were to construe "culturing" as a step-plus-function limitation, it would run the risk of interpreting the process claim of the '349 patent in a way that Congress never intended, rendering the scope of coverage of the patent uncertain and disrupting the patentee's settled expectations regarding the scope of the claims. *Masco*, 303 F.3d at 1328; *O.I. Corp.*, 115 F.3d at 1583.

5. Conclusion and Claim Construction

Accordingly, the Court rules that claim 7 of the '349 patent does not contain a step-plus-function limitation and that the regular framework for assessing infringement therefore applies.[69]

IV. VALIDITY CHALLENGES UNDER 35 U.S.C. § 112

When claims are construed broadly, alleged infringers commonly challenge validity under 35 U.S.C. § 112, ¶¶ 1, 2 in light of the broad construction. *Amgen II*, 314 F.3d at 1330. This is exactly what HMR/TKT does here. It argues that certain of Amgen's claims are now invalid because of how broadly the Court construed them. Because these validity challenges relate directly to this Court's claim construction and claims are construed the same way for both invalidity and

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[69] Thus, as with the '698 patent, the procedural dispute and the Court's conclusion as to whether HMR/TKT should be allowed to raise this argument are moot.

infringement, *see, e.g.*, *W.L. Gore & Assocs., Inc.*, v. *Garlock, Inc.*, 842 F.2d 1275, 1279, 1280 (Fed. Cir. 1988), this Court now addresses the relevant section 112 issues before turning to the infringement issues. *See Amgen II*, 314 F.3d at 1330 (addressing section 112 issues before infringement for the same reasons).

As with any validity challenge, the Court begins by presuming that the patents are valid. *Amgen II*, 314 F.3d at 1335; 35 U.S.C. § 282 (2000).[70] As a result, HMR/TKT bears the burden of going forward and a "heavy burden" of persuasion, one that requires proof by clear and convincing evidence. *Amgen II*, 314 F.3d at 1335. Clear and convincing evidence is "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions is 'highly probable.'" *Buildex, Inc.* v. *Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988).

A. Definiteness

1. The '698 and '349 Patent[71]

a. Discussion

Paragraph 2 of section 112 requires that a patent specification include one or more claims "particularly pointing out and distinctly claiming subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2 (2000). The Federal Circuit has stated that the standard for determining whether a claim is sufficiently definite is "[i]f one skilled in the art would understand the bounds of the claim when read in

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[70] As remarked in *Amgen I*, 126 F. Supp. 2d at 137, the presumption of validity is not a true evidentiary presumption. Instead, it shifts the burden of proof to the non-patent holder and places on it not only the burden of going forward but also the burden of persuasion.

[71] Generally, the Court addresses each argument patent by patent. Where, as here, it makes sense to address more than one patent at once, due to their similarities, the Court will do so.

light of the specification." *Exxon Research and Eng'g Co.* v. *United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001); *Union Pac. Res. Co.* v. *Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001) ("The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification."). Although the definiteness requirement is meant to protect public notice of the scope of the patentee's right to exclude, *Honeywell Int'l, Inc.* v. *Int'l Trade Comm'n*, 341 F.3d 1332, 1338-39 (Fed. Cir. 2003), the Federal Circuit has made clear that the standard for indefiniteness is rather high. A claim is not indefinite merely because its scope is not ascertainable from its face. Instead, it is indefinite if it is "insolubly ambiguous and no narrowing construction can be properly adopted." *Amgen II*, 314 F.3d at 1342; *Honeywell*, 341 F.3d at 1338-39; *Amgen Inc.* v. *Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991); *Standard Oil Co.* v. *Am. Cyanamid Co.*, 774 F.2d 448, 453 (Fed. Cir. 1985).

HMR/TKT argues that under the Court's construction of "DNA encoding" the asserted claims of the '698 patent and claim 7 of the '349 patent are invalid as indefinite because they include within their scope many embodiments that will not make EPO. HMR/TKT's Opening Br. After Trial [Doc. No. 808] at 47-48. Specifically, it argues that the Court's construction of the term requires only that the DNA provide the requisite letters or codons, regardless of what protein is actually made, and that the evidence demonstrates that while many cells contain the same DNA codons, only those in which certain particular DNA codons are contiguous will actually produce EPO. Further, it asserts that Amgen has changed its stance and now claims that "genetic instructions for" includes not only the codons but also the splicing instructions for putting those codons together in the correct order.[72]

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[72] The Court notes that it did not construe the term to include the splicing instructions for putting the codons together. That being said, the term

The claims, it asserts, say nothing about splicing instructions or messages and, as such, are indefinite and inoperative.

Amgen responds primarily by arguing that the evidence demonstrates that skilled artisans using the teachings of Amgen's patents would have been able to produce EPO using cells comprising non-contiguous DNA encoding the "mature erythropoietin amino acid sequence of FIG. 6." Amgen's Reply to HMR/TKT's Opening Br. After Trial [Doc. No. 815] at 33-34.[73] Further, it claims that this very evidence establishes that those skilled in the art would have known how to determine which processes fell within the '698 and '349 claims.

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does not occur in a vacuum. It is read with reference to "the mature erythropoietin amino-acid sequence depicted in Figure 6 of the patent." Thus, the claims themselves communicate that other steps are necessary to result in the correct order of amino acids.

[73] Amgen also argues that this Court stated during the 9/18/03 motion hearing that it was not going to address any issues that were not remanded to the Court by the Federal Circuit. Amgen's Reply to HMR/TKT's Findings of Fact [Doc. No. 816] at 173. The issue of infringement, however, was remanded to this Court. A complete decision regarding infringement necessarily includes analysis of these defenses. Moreover, neither party contended that the Court ought not construe "DNA encoding." To the contrary, both parties made it clear this term needed construction. As a result of that construction, a door to a new validity challenge was opened. Thus, to do its job adequately, the Court must address HMR/TKT's challenge.

Additionally, Amgen points out that this Court held that the cell claims (1, 3, 4, and 6) of the '349 patent are adequately described and enabled, and that these rulings are law of the case. Amgen's Reply to HMR/TKT's Opening Br. at n.150. Claim 7 contains a "DNA encoding" limitation only through its dependence from claims 1 and 3. *Id.* As such, Amgen contends, any invalidity challenge to the '349 patent must address the only addition claim 7 makes, which is the "growing step." Thus, Amgen reasons, HMR/TKT's challenge regarding "DNA encoding" should fail. This procedural argument, however, need not be addressed, given the Court's ultimate finding, discussed below, that claim 7 of the '349 patent is not invalid for indefiniteness.

The primary dispute, then, is whether the specification teaches skilled artisans to splice the codons into the correct order when the codons are not contiguous but need to be in order to make EPO. If it does, then the claims are not indefinite as they do not cover embodiments that do not make EPO.

While it may be true, as Dr. Kingston originally stated, that "only those cells in which the DNA letters were contiguous would actually produce EPO," Kingston Test., R. Trial Tr. at 56-60, 164: 2-7, Dr. Kingston admitted that the cells from Example 10 of Amgen's specification produce EPO even though the Figure 6 codons for the mature erythropoietin sequence in the Example 10 cells are not contiguous. *Id.* at 164: 8-22; 170: 4-10. Either Dr. Kingston was blatantly contradicting his original statement, or—as the Court concludes is more likely—Example 10 and Figure 6 communicate to Dr. Kingston, one skilled in the art, how non-contiguous codons can be manipulated to produce EPO. This belies HMR/TKT's argument that the claims are vague or indefinite for not including splicing instructions and for covering contiguous and noncontiguous codons because the specification provides the information that Dr. Kingston believed was missing from the claims.

This deduction—that the specification makes the term "DNA encoding" understandable to the skilled artisan, *Exxon Research and Engineering Co.*, 265 F.3d at 1375; *Union Pacific Resources Co.*, 236 F.3d at 692—is supported by expert testimony from Dr. Lodish and by other testimony from Dr. Kingston.

According to Dr. Lodish, Dr. Lin's patent taught those skilled in the art in 1983 to produce DNA sequences encoding EPO that are either contiguous or *noncontiguous*. Lodish Test., R. Trial Tr. at 1061: 4-1063: 4. In other words, Dr. Lodish testified that those skilled in the art would not consider the phrase "DNA encoding" to require the presence of contiguous codons of the mature EPO sequence of Figure 6.

The main support for this contention stems from the fact that the codons were noncontiguous in Figure 6 of the patent. As mentioned earlier in the claim construction portion of this memorandum and order, Dr. Lodish testified that those of ordinary skill in the art at the time would have understood the disputed term to mean "a DNA which when copied into RNA, and *if necessary* spliced, specifies the order of amino acids that are the mature erythropoietin amino-acid sequence depicted in Figure 6 of the patent." Lodish Test., R. Trial Tr. at 1054: 17-22 (emphasis added); *id.* at 1058: 10-1059: 3. He explained that Figure 6 disclosed to those skilled in the art the codons for the mature EPO amino acid sequence, the introns, exons, and splice donor and acceptor sites of the human genomic EPO sequence. *Id.* Indeed, Dr. Kingston admitted that Lin's specification discloses the EPO gene sequence, the EPO splice donor and acceptor sites, and the linkage of a non-human promoter with the EPO gene. Kingston Test., R. Trial Tr. 116: 23-117: 2. According to Dr. Lodish (and not directly disputed by Dr. Kingston), this information, along with what was known in the art, enabled skilled artisans to alter the codons, to alter or eliminate the introns, and to make many DNA sequences that would encode human EPO and work in the claimed processes. *Id.* Thus, contrary to HMR/TKT's assertions, expert testimony from both sides shows that those skilled in the art would understand the claims to cover contiguous and non-contiguous DNA sequences that when necessary could be spliced into a correct and contiguous order to produce EPO. *Union Pacific Resources Co.*, 236 F.3d at 692 ("The definiteness inquiry focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification.").

b. Conclusion

HMR/TKT has failed to establish by clear and convincing evidence that "DNA encoding" is a vague, ambiguous, or

undefined term not understandable to a skilled artisan when read in light of the specification. Accordingly, the Court rejects HMR/TKT's argument that the disputed claims of the '349 and '698 patent are indefinite.

B. Written Description[74]

1. The '698 and '349 Patents

a. Discussion

The basic requirements for the content of a patent specification are found in 35 U.S.C. § 112, ¶ 1:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . .

35 U.S.C. § 112, ¶ 1 (2000). "The purpose of this provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin* v. *Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000). Therefore, the specification must communicate clearly to those skilled in the art that the inventor invented what is claimed. *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Specifically, the disclosure as originally filed must explicitly or inherently convey to the skilled artisan that the inventor had possession at that time of the later claimed subject matter. *Reiffin*, 214 F.3d at 1346; *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); *see generally* Guang Ming

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[74] For a discussion of the controversy within the Federal Circuit as to whether section 112 contains a separate written description requirement, or whether it only contains an enablement requirement, see Vernon M. Winters & Elizabeth Stotland Weiswasser, *The Written Description Requirement: Ripe Enough? Or Is More Percolation Required*, Fed. Law., Aug. 2004, at 20.

Whitley, *A Patent Doctrine without Bounds: The "Extended" Written Description Requirement*, 71 U. Chi. L. Rev. 617 (2004). Compliance, however, is to be judged as of the date the application is filed. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1251 (Fed. Cir. 1989); *Application of Koller*, 613 F.2d 819, 824 (C.C.P.A. 1980). Thus, the critical inquiry is whether the specification clearly communicated to those skilled in the art what was claimed based on what was known in the art at the time of the filing—in this case, 1983-84. Only if the claims would have been, at the time of filing, correctly rejected for inadequate support will a court find that the claims are now invalid for lack of support. *See Koller*, 613 F.2d at 824.

HMR/TKT contends that Amgen's claims, as construed by the Court, have a scope far greater than the written description of Amgen's patents and are, therefore, invalid. HMR/TKT's Opening Br. After Trial at 47-48. Primarily, it makes two arguments in support of this contention. First, HMR/TKT argues that the specification "repeatedly describes [the] DNA, cells, processes and proteins in terms of *only* exogenous DNA and heterologous recombination," whereas the Court construed the asserted claims in the '698 and '349 patents to cover both exogenous and endogenous DNA and homologuous and heterologous recombination.[75] HMR/TKT's Opening Br. After Trial at 47-48. Second, HMR/TKT points to the undisputed fact that the specification provides only an example of a process which places the promoter just upstream of the ATG initiation codon of a cloned and isolated EPO gene,

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[75] This is the same argument that HMR/TKT made during the first trial and on appeal with reference to the product claims of the '422 and '349 patents. *Amgen I*, 126 F. Supp. 2d at 149-150, 154 n.51 (rejecting the argument); *Amgen II*, 314 F.3d at 1331 (same). Since the asserted claims of the '698 and claim 7 of the '349 patent are process claims, however, HMR/TKT urges that this argument now has merit and ought be revisited in this context.

although the Court construed "operatively linked," as found in the '698 patent,[76] to cover placement much farther upstream. *Id.*[77] As such, HMR/TKT argues, the asserted process claims of the '698 patent fail to provide adequate written description. *Id.*

(1) HMR/TKT's First Argument: Endogenous DNA and Homologous Recombination

Although HMR/TKT's first argument is, in part, factually correct—the specification explicitly discloses only exogenous EPO DNA expression systems and heterologous recombination techniques[78]—it is misdirected. The section 112 inquiry focuses on what was known by those skilled in the art at the time of the filing of the application. Here, it is undisputed that in 1983-84 (the time period of the application filing date), endogenous activation technology and homologous recombination were not known to skilled artisans. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34- 35.[79] Therefore, this technol-

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[76] The term "operatively linked" is not found in the '349 patent, so this argument only relates to the '698 patent.

[77] In *Amgen I*, the Court construed "operatively linked" to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen I*, 126 F. Supp. 2d at 90. It refused to read any distance restriction in the claim term "operatively linked."

[78] As stated in *Amgen I*, experts for both sides agreed that the specification did not explicitly show any examples of human EPO production whereby endogenous EPO DNA was expressed. 126 F. Supp. 2d at 150 n.50. The Court thus inferred that "Amgen did not in fact contemplate applying its techniques to effectuate endogenous DNA expression." *Id.*

[79] HMR/TKT does not dispute Amgen's contentions (see Amgen's Reply to HMR/TKT's Opening Brief After Trial at 34-35) that these are post-filing advancements. Moreover, in making its reverse doctrine of equivalents argument, HMR/TKT asserted that this difference contributed to the Court's finding that HMR 4396 was "technologically advanced."

ogy is irrelevant to the written description analysis, and for good reason. "If later states of the art could be employed as a basis for rejection under 35 U.S.C. § 112, the opportunity for obtaining a basic patent upon early disclosure of pioneer inventions would be abolished." *Application of Hogan*, 559 F.2d 595, 606 (C.C.P.A. 1977); *see also Koller*, 613 F.2d at 825 (same).[80]

HMR/TKT incorrectly assumes that the Court's construction of Amgen's claims to cover this later developed technology changes the analysis. *Application of Koller*, a case similar to this one, shows the fallacy of HMR/TKT's assumption. In that case, the Federal Circuit upheld a broad construction of the term "liquid medium" that covered all solvents (including the later developed water-immiscible solvents) despite a specification that only described water and water-miscible

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HMR/TKT's Mem. in Opp'n re '698 at 6; *see Amgen I*, 126 F. Supp. 2d at 104. Indeed, the Court found in *Amgen I*, and the Federal Circuit affirmed, that endogenous activation was a later-developed technology. *Amgen I*, 126 F. Supp. 2d at 160; *Amgen II*, 314 F.3d at 1334 (noting that Amgen could not have described the endogenous activation method because it was developed 10 years later).

[80] Professor John F. Duffy has recently suggested an intriguing revision to the "prospect theory" of patents, which justifies "prospect patents"—"broad patents issued in the early stages of technical development"—on the ground that they create social benefit by encouraging investment in a technological prospect after the property right has been granted, rather than by encouraging the investment that led to the patent in the first place. John F. Duffy, *Rethinking the Prospect Theory of Patents*, 71 U. Chi. L. Rev. 439, 440 (2004). Professor Duffy agrees that "prospect patents" are socially beneficial in a forward-looking way, but for a different reason: they channel rivalry in such a way that the property right goes to the inventor who is willing to accept the least profit for it. *See id.* at 443-44. Because patents have fixed terms, obtaining a patent earlier in the technological development process means that the period between the date when the patentee can convert the invention into a marketable product and the date when the patent term ends (and hence the period when the property right will actually generate profit) will be shorter. *See id.*

solvents—and not water-immiscible solvents. It reversed, however, the decision of the United States Patent and Trademark Office Board of Appeals that had found, *inter alia*, that the claims failed to provide adequate description. The Federal Circuit conducted its section 112 analysis based on what was claimed and known at the time of the application filing date. Because water-immiscible solvents were not known at the time of the application filing date, the Federal Circuit found that the term "liquid medium" was adequately described. *Koller*, 613 F.2d at 823-25.

Here, the situation is very similar. Because homologous recombination and use of endogenous DNA were not known to those skilled in the art at the time of the application, HMR/TKT's first argument for inadequate written description fails. As the Federal Circuit explained in *Application of Hogan*, "the Courts have consistently considered subsequently existing states of the art as raising questions of infringement but never of validity." *Hogan*, 559 F.2d at 607 (noting that the PTO's concern that allowance of the claims might lead to enforcement efforts against later developers is "both irrelevant and unwarranted" because "[t]he business of the PTO is patentability, not infringement"); *United States Steel Corp.*, 865 F.2d at 1251 (stating that the fact that "claim[s] may cover a later version of the claimed [invention] relates to infringement not to patentability").

HMR/TKT's arguments are more properly reserved for invoking the judicially developed reverse doctrine of equivalents defense which allows interpretation of the claims in light of the specification, *inter alia*, and precludes improper enforcement against later developers. *Hogan*, 559 F.2d at 607. This argument alone fails to establish this defense. Because this is the only argument presented with respect to the sufficiency of the written description of claim 7 of the '349 patent, the Court holds that HMR/TKT has failed to meet its burden with respect to this defense.

(2) HMR/TKT's Second Argument: Placement of the Promoter

HMR/TKT's second argument and Amgen's response thereto, as they relate to the '698 patent, render determination of the written description a bit more squirrelly. As stated above, HMR/TKT correctly argues that the specification only describes insertion of the promoter just upstream of the ATG initiation codon of the EPO gene to be expressed while the Court construed the claims to cover HMR/TKT's process of inserting the promoter far upstream leaving multiple ATGs between the promoter and the gene to be expressed.[81] Instead of counter-arguing, as it did in response to HMR/TKT's first argument, that HMR/TKT's placement technique was a post-filing advance which need not be described, Amgen contends that by 1984, artisans of ordinary skill could have placed a promoter DNA in such a position that multiple ATGs would exist between it and the gene to be expressed, and they knew how to express proteins in vertebrate cells by positioning a promoter upstream of exon coding sequences and removing unwanted DNA by manipulating splice sites. Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34-35; Amgen's Reply to HMR/TKT's Findings of Fact ¶ 67. Further, Amgen asserts, evidence shows that those of skill in the art would have understood the patent to describe operative linkages of far greater distances than 44 pairs and that skilled artisans would have understood from Lin's patent how to avoid potentially interfering ATG sequences and thereby successfully position the promoter further upstream of DNA encoding EPO. *Id.* ¶ 68, ¶ 342.[82]

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[81] *See Amgen I*, 126 F. Supp. 2d at 103-104 (finding that the specification discloses the promoter placement at a position forty-four base pairs from the first codon that expresses the leader peptide leaving only one ATG in the region to be expressed).

[82] Amgen also argues that the Court's findings regarding proximity of the promoter concern the process for constructing cells (cells which been

This argument is curious because the easier path would have been to argue that placement so far upstream was a post-filing advance. Indeed, the Court's factual findings in *Amgen I* would have supported such an argument. *See, e.g., Amgen I*, 126 F. Supp. 2d at 160 (concluding that placing the promoter farther upstream works to make HMR/TKT's process more "technologically advanced" than that in Amgen's patent and commenting that there was no evidence implying that "one of ordinary skill in the art would dare to place a promoter sequence in such a position that multiple ATGs would exist between it and the gene to be expressed"). Such an argument, however, would have weakened Amgen's position with respect to the reverse doctrine of equivalents. In other words, urging that this technique was a post-filing advance would work against Amgen's argument that HMR/TKT's product and process is not so far changed in principal that the Court ought find that it does not infringe under the reverse doctrine of equivalents.

Stuck in a similar catch-22, HMR/TKT argues with respect to section 112 that Amgen should have described upstream placement of the promoter, yet, in furtherance of its reverse doctrine of equivalents argument, HMR/TKT argues with equal passion that a process for producing EPO by linking the promoter and transcription control sequences far upstream of the EPO gene had never been done before HMR/TKT

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held to be adequately described and enabled) and are, therefore, irrelevant to the '698 and '349 claimed processes for producing EPO. Amgen's Reply to HMR/TKT's Opening Br. After Trial at 35; Amgen's Reply to HMR/TKT's Findings of Fact at 41. This argument fails. Just because the cells themselves and the EPO product were found to be adequately described and enabled by the product claims does not mean that the method by which the cells are constructed or the EPO is made is necessarily adequately described and enabled in the process claims. As this Court pointed out in *Amgen I*, "[a] product patent claims a structural entity that, though some process must be undertaken in order to create it, is in no way defined or limited by how it is made." 126 F. Supp. 2d at 101.

developed its patented gene activation process. HMR/TKT's Reply Br. After Trial [Doc. No. 819] at 29, 34. Further, it argues that those skilled in the art recognized that promoter linkages further upstream of the initiation codon would *not* work to produce EPO. HMR/TKT's Findings of Fact ¶ 493. Thus, HMR/TKT's reverse doctrine of equivalents argument belies its argument that Amgen should have described placement of the promoter further upstream of the EPO gene to be expressed since, according to HMR/TKT, this had never been done before. Thus, both parties, to a degree, have argued against their best interests on this issue because to do otherwise would weaken their positions with respect to application of the reverse doctrine of equivalents.

However the parties may frame the issue, this Court, as trier of fact in this case, must determine whether placing the promoter farther upstream was a concept sufficiently known to those skilled in the art at the time of filing such that the claims would have been understood to encompass such a technique. *United States Steel Corp.*, 865 F.2d at 1251 ("'[L]anguage in a specification is to be understood for what it meant to one having ordinary skill in the art at the time the application was filed' . . . and . . . support need be found for only the claimed invention, in view of how one skilled in the art at that time would construe the claims and would read its specification." (quoting *Koller*, 613 F.2d at 824) (internal citation omitted)); *United States Steel Corp.*, 865 F.2d at 1252 (considering the state of the art in 1983-84, the level of sufficiency and the condition of knowledge about all art-related facts at the time of filing).[83] If the Court determines

[83] While the Court found in the first trial that HMR/TKT's promoter placement was a "technological advance" over Amgen's process, the Court notes that it did so in a different context under a different burden of proof and that the ultimate holding of the Court was reversed. In *Amgen I*, the Court held that HMR/TKT had shown by a preponderance of the evidence that its process was substantially different from the process identified in Amgen's '698 patent and claim 7 of the '349 patent. *Amgen I*, 126

that this is so, the Court must consider whether the specification in its entirety—not just literally—conveys to the skilled artisan that Amgen's process includes such upstream promoter placement. *Kaslow*, 707 F.2d at 1375; *cf. Application of Edwards*, 568 F.2d 1349, 1352 (C.C.P.A. 1978).

After careful review of the evidence from the first and second trials, the Court now concludes that placement of the promoter further upstream of the EPO coding region and splicing out deleterious ATGs was indeed a concept known and understood—albeit not practiced—by those skilled in the art at the time Amgen filed its application (1983-84).

Dr. Lodish and Dr. Kingston testified that both Amgen and HMR/TKT use a technique of linking two different pieces of DNA together with a splice donor site and a splice acceptor to express a protein and that this was a standard technique in 1983. Kingston Test., Trial Tr. at 1428-30, 1433, 1434: 12-19; Lodish Test., R. Trial Tr. at 1081 (claiming that at the time of the patent application this type of splicing was common). While Dr. Lodish did indeed admit that Dr. Lin did not know what sequences were upstream of the EPO gene, and

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F. Supp. 2d at 103-104, 122. This ruling was based not only on a finding regarding the promoter placement but also on the finding that HMR/TKT uses homologous recombination as opposed to heterologous recombination. Therefore, the factual finding regarding promoter placement was not alone determinative (as it is here). The Court's legal conclusions based on these factual findings were reversed by the Federal Circuit. Further, the burden here is on HMR/TKT to show by clear and convincing evidence (as opposed to proof by a fair preponderance) that the asserted claims are invalid. Lastly, because the reverse doctrine of equivalents was before the Court for the first time on remand, this Court explained to the parties that it would be evaluating, or rather re-evaluating, the issues involved in such an argument, such as whether placement of the promoter was indeed truly novel. *See* R. Trial Tr. at 1080-81 (noting its previous findings with respect to placement of the promoter, the Court explained that this issue "cuts to the heart" of the reverse doctrine of equivalents and allowed evidence on the issue).

that it was intuitive to place the promoter close to the EPO coding region because the "longer the distance the more problems you're likely to encounter," he clarified that those skilled in the art knew that it was possible to vary the distance and still cause transcription and proteins to be made, because the sequences that are unwanted are readily identifiable and can be avoided. Lodish Test., Trial Tr. at 255-58. Further, he explained, those skilled in the art in 1983 did indeed know that a promoter could be placed 8,000-10,000 bases upstream and that very long intervening sequences could be spliced out. Lodish Test., R. Trial at 1081. Even Dr. Kingston himself admitted that in 1983 those skilled in the art knew how to place a promoter much further upstream than 44 base pairs, the location identified in Example 7 of Dr. Lin's patent. Kingston Test., Trial Tr. at 1436-38.

Additionally, there were published articles showing that those skilled in the art possessed this knowledge. Dr. Kingston's mentor, Dr. Sharp, published an article in 1983 that, according to Dr. Kingston, showed a construct in which a splice donor site was added to splice out approximately a 700 base pair fragment of DNA ("a 5 prime splice and a 3 prime splice") from the message. Kingston Test., Trial Tr. at 1435-36. Indeed, Dr. Kingston himself published an article in 1982 that disclosed that the way to discard a portion of the DNA that was not wanted in the vector was to put a downstream splice receptor or acceptor site and splice it out. *Id.* at 1436-37. In the constructs discussed in the article, the distance between the 5 prime and 3 prime splice sites was, according to Dr. Kingston, between 180 and 500 pairs. *Id.* at 1438.

HMR/TKT argues, however, that the evidence shows that no one had in fact used those splice sites the way that HMR/TKT eventually did—in other words, that placing the promoter upstream as HMR/TKT did was novel. HMR/TKT's Response to Amgen's Findings at 130. HMR/TKT also sug-

gests that the situations to which reference has just been made appear only in nature; that is, they were not human constructs or experiments. *See, e.g.*, Lodish Test., R. Trial Tr. at 1104: 15-1105: 5. The Court is not persuaded that the evidence shows what HMR/TKT claims it does. First, Dr. Sharp's article, Trial Ex. 247, discloses actual experiments showing upstream placement, *see, e.g.*, R. Trial Tr. at 1134-35. HMR/TKT produced no evidence to the contrary. Tellingly, HMR/TKT's counsel neither asked Dr. Kingston whether actual experiments had been conducted in 1983-1984 nor asserted in any of its post-trial memoranda the absence of actual experimentation. Second, and perhaps most enlightening, the only support HMR/TKT offers for its contention that no one skilled in the art had in 1983-84 placed the promoter upstream as HMR/TKT did, or even would have *dared* to do so, is the Court's previous factual findings, which were made with respect to a different legal issue. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 15 (citing only this Court's opinion in support); HMR/TKT's Reply Br. After Trial at 29 (citing this Court's opinion and unsupportive testimony by Dr. Lodish (inaccurately referred to as "Kingston Tr. 162-167") and irrelevant testimony by Dr. Kingston, "Kingston R. Tr. 177, 181"); HMR/TKT's Proposed Findings of Fact ¶¶ 111, 112, 114, 116 (citing this Court's opinion and irrelevant testimony from Dr. Lodish, admitting that he did not include *homologous recombination* in the first edition of his textbook). The Court finds that placement of the promoter further upstream, as HMR/TKT does with its HMR 4396, was a technique known to those skilled in the art at the time of Amgen's application filing.[84]

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[84] In any case, even if the Court were to conclude, as HMR/TKT urges, that no one then had the courage to use the splice sites as HMR/TKT later did, HMR/TKT's written description challenge would still fail; if the courage *and knowledge* had been missing and HMR/TKT's placement of the promoter had been truly innovative and new, then this technique

Because upstream placement of the promoter was known at the time of Amgen's application, however, the Court now addresses whether HMR/TKT has shown by clear and convincing evidence that Amgen did not adequately describe such a placement. The Court agrees with HMR/TKT's central contention that the specification explicitly refers only to placement of the promoter in close proximity (within 44 base pairs) of the EPO gene to be expressed, leaving only one ATG adjacent to the amino terminal coding region. '933 Patent, Ex. 1, col. 24: 15-32. "The test for determining compliance with the written description requirement," however "is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter," rather than the presence or absence of literal support in the specification for the claim language. *Kaslow*, 707 F.2d at 1375; *cf. Edwards*, 568 F.2d at 1352 (noting that in the context of the case before it, "this translates into whether the parent application provides adequate direction which reasonably leads persons skilled in the art to the later claimed compound"). After much reflection and despite some hesitancy, the Court concludes that the disclosure does convey the "later claimed subject matter."

First, as Amgen rightly points out, the '698 claims themselves have no limitations specifying the promoter distance or the number of ATGs. Instead, the claims state that the promoter DNA must be "operatively linked" to the "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." The Court in *Amgen I* construed this to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen I*, 126 F. Supp. 2d at 90.

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would have constituted a post-filing technological advance—something Amgen need not have described in order to satisfy section 112, paragraph 1.

Second, as was determined in *Amgen I*, the specification does not clearly communicate a locational restriction. *Amgen I*, 126 F. Supp. 2d at 90. That the specification recites in one of the examples an exact location for the promoter that is in close proximity to the EPO gene to be expressed is not dispositive. "[T]hat a claim may be broader than the specific embodiment disclosed in a specification is of no moment." *In re Rasmussen*, 650 F.2d 1212, 1215 (C.C.P.A. 1981); *see Gentry Gallery, Inc.* v. *Berkline Corp.*, 134 F.3d 1473, 1480 (Fed. Cir. 1998). As the Court of Customs and Patent Appeals reasoned in *In re Kirschbraun*, 44 F.2d 675 (C.C.P.A. 1930), a court "should never interpret a positively recited generic expression [such as "operatively linked"] to the precise instrumentality disclosed by the patent, except where such narrow interpretation is necessary to distinguish the claim from prior art." *Id.* at 739 (internal citations and quotations omitted).[85]

The only support in the specification that the invention is of a narrower scope than the claims is the absence of specific examples showing an alternate location for the promoter. The specification, however, does not limit the patent to the examples therein. It does not clearly identify placement within 44 base pairs as the only possible location from which to conduct the process nor does it indicate that this exact location was an essential element of the invention or that placement farther upstream is "outside the stated purpose of the invention." *Cf. Amgen II*, 314 F.3d at 1334 (considering these factors); *Gentry*,

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[85] Although the Court intimated in *Amgen I* that the written description requirement may be different for process claims as opposed to product claims, 126 F. Supp. 2d at 150, case law indicates that the written description inquiry is conducted in the same manner regardless of whether the claims address a product or a process. *See, e.g., Rasmussen*, 650 F.2d at 1212 (applying same section 112 analysis to method claim as applied by other courts with respect to product claims); *see also In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976); *Koller*, 613 F.2d at 819.

134 F.3d at 1479 (same); *Ethicon*, 93 F.3d at 1582 (considering whether the aspect was considered an element of the invention and stating that if it was not then the patentee was free to draft the claim broadly). Moreover, the specification does not address possible variations from which the Court could conclude that a further upstream placement was not in the realm of possibility.

That Amgen chose to show placement of the promoter in very close proximity is only evidence that this was perceived to be the best location to achieve operative linkage—as Dr. Lodish testified—not the only location. Lodish Test., Trial Tr. at 258 (explaining that the longer the distance the higher likelihood that problems might occur and that "there's no reason one would want to put it very far upstream. But one could," with a little bit of work); *id.* at 553 (commenting that "in practice in the laboratory one does what is most expeditious"); Lodish Test., R. Trial Tr. at 1131 (explaining that Dr. Lin had no reason even to consider other sequences of pieces of DNA); *cf.* Kingston Test., R. Trial Tr. at 41: 20-21 (testifying that standard practice in 1984 was to place the promoter in a position such that there was not another ATG present). True, Dr. Lodish stated that the patent teaches that by *linking* a strong promoter or *placing it near* the first codon for the signal sequence of EPO, one could overcome the natural suppression of EPO expression in vertebrate cells. Lodish Test., R. Trial Tr. at 1070, 1077- 78. This, however, does not unambiguously limit the location of the promoter to a distance of 44 base pairs or indicate that further upstream placement was not part of the invention. As Dr. Lodish explained, placement of the promoter thousands of base pairs upstream, as HMR/TKT does, is only a "minor difference" that is "irrelevant in the final process." *Id.* at 1077: 1-6.[86] Thus, as

[86] Dr. Lodish also conceded that placement of the promoter can indeed affect expression, Lodish Test., Trial Tr. at 421; *cf.* Kingston Test., R. Trial Tr. at 44: 20-45: 1-5. He clarified, however, that the difference in

testified to by Dr. Lodish, the specification teaches that putting a strong viral promoter upstream of the human EPO gene is the important feature—not how far upstream—as long as the intervening sequences are spliced out. Lodish Test., Trial Tr. at 173, 549; *see also* Lodish Test., R. Trial Tr. at 1081 (noting that "there's nothing different about a large intron spliced out and a small intron spliced out"); *Cooper Cameron Corp.* v. *Kvaerner Oilfield Products, Inc.*, 291 F.3d 1317, 1322-23 (Fed. Cir. 2002) (considering expert testimony on the issue of what the specification teaches). In other words, Amgen's patent teaches that the natural suppression of EPO expression in vertebrate cells can be overcome by *operatively linking* a nonhuman promoter *upstream* of DNA encoding human EPO. *See id.*; *see also* Lodish Test., R. Trial Tr. at 1068: 21-1070: 3.

Therefore, the Court infers that though the examples may show linkage that is *directly* upstream, those skilled in the art would not, nor does the Court, read the specification so to limit the process. *United States Steel Corp.*, 865 F.2d at 1251; *cf. Ethicon*, 93 F.3d at 1582 n.7 (noting that 35 U.S.C. § 112 (1994) allocates to the inventor the task of claiming what the inventor regards as his invention); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1565 (Fed. Cir. 1991) ("There is no legally recognizable or protected essential element, gist or heart of the invention in combination patent. The invention is defined by the claims." (citations and internal quotation marks omitted)). As such, Amgen was free to draft the claim broadly (within the limits imposed by prior art) to exclude the exact placement of the promoter as a limitation of the claimed invention. *Cf. Ethicon*, 93 F.3d at 1582 n.7. "Such a claim is not necessarily unsupported by the specification even though

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expression is determined not by the number of pairs between the promoter and the EPO gene necessarily but by other factors concerning the general area of the chromosome in which it finds itself. Lodish Test., Trial Tr. at 420-421.

it would be literally infringed by undisclosed embodiments." *Id.*

Third, although HMR/TKT has shown that the specification lacks literal support for a process that places the promoter further upstream, it has failed to show by clear and convincing evidence that Amgen's patent does not "reasonably convey to the artisan that [Amgen] had possession at that time of the later claimed subject matter." *Kaslow*, 707 F.2d at 1375 (noting that the presence or absence of literal support in the specification is not determinative). To the contrary, the evidence shows that the specification (both the written words and the figures) discloses the techniques that are employed in a process that places the promoter further upstream such as HMR/TKT does in HMR 4396.[87] It is undisputed that the specification discloses a DNA sequence and the amino acid sequence it encodes, introns, exons, splice donor and splice acceptor sites, and the linkage of a nonhuman promoter with the EPO gene, and communicates that splicing events occur to avoid the deleterious effects of ATGs and to allow the appropriate final functional mRNA to form to produce the amino acids disclosed in Figure 6. *See, e.g.*, Kingston Test., Trial Tr. at 1428-29, 1430; Kingston Test., R. Trial. Tr. at 116: 23-117: 2; *see also* Lodish Test., R. Trial Tr. at 1061: 4-1063: 4. As discussed *infra* with respect to the reverse doctrine of equivalents, the evidence shows (albeit by a slim margin) that HMR 4396 uses the same splice donor and splice acceptor sites as are disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25.[88] HMR/TKT merely copies the

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[87] The Court refers to HMR 4396—as an example of a process that places the promoter further upstream—to support the conclusion that the specification communicates to those skilled in the art a process that incorporates such upstream placement.

[88] While there was much debate about this subject, as discussed in more detail *infra* (parts V.A.3-4, V.B.4), the Court credits Dr. Lodish's

splice donor site and places it upstream of the deleterious ATGs, the intended effect of which is to splice out all the deleterious ATGs that were upstream of the coding region of the EPO gene. *Id.* (explaining that the way the splice donor site is moved is by "ma[king] a design that happens to include the same nucleotides" and "the purpose of that is so that this splice donor . . . would direct a splicing event" that spliced out all of the deleterious ATGs); *see also* Lodish Test., R. Trial Tr. at 1081 ("Very simply put, what [HMR/]TKT did is take this splice donor that's right here, include this G residue directly upstream of it, and move it in toto immediately adjacent to this hGH signal sequences. So in fact, the splicing that occurs . . . in the RNA, between donor 1 and acceptor 1 is identical to the splicing that occurs in . . . Amgen's Example 10 cells."); Lodish Test., Trial Tr. at 174; Lodish Test., R. Trial at 1076: 23-1077: 6; *id.* at 1068-69 (discussing the three principals of Lin's '698 patent). As discussed earlier, placement of the promoter further upstream and splicing out deleterious data was a technique known to skilled artisans in 1983-84. Thus, Amgen's process discloses exactly what HMR/TKT's process does, that is, it discloses locating a strong

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testimony explaining that the exons are not included when one skilled in the art refers to the splice donor and acceptor sites. Lodish Test., R. Trial Tr. at 1107-1110; *id.* at 1132-33 (explaining that it is the splice donor sequence, not the splice junction, that will determine where downstream and with what corresponding DNA downstream a splice junction will splice, and stating that "the splice donor is the sequence . . . that is removed during the splicing process," the splice acceptor is the sequence that is removed downstream, and "it's the regions on either side that are linked together."). There is testimony by Dr. Kingston and evidence from the HMR/TKT's IND that supports this conclusion. As a result, the Court concludes that HMR 4396 uses the same splice donor site as that disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25 (admitting that absent the exons, the splice donor sites were the same and that the intended effect was to splice out what is in between, including intervening sequences and the deleterious ATGs).

promoter upstream of the ATG initiation codon of a cloned and isolated EPO gene (i.e., upstream of the DNA encoding EPO), and splicing out the deleterious data. *Gosteli*, 872 F.2d at 1012 (explaining that the specification must communicate clearly to those skilled in the art that the inventor invented what is claimed).

While it appears that the scope of the right to exclude as set forth in the claims does not overreach the scope of Amgen's contribution to the field of the art as described in the specification, *see Reiffin*, 214 F.3d at 1346, HMR/TKT points to one piece of evidence that suggests the contrary and gives the Court pause. As discussed earlier in a different context, Dr. Lodish admitted that Dr. Lin never even attempted such an upstream placement and did not know what was upstream or downstream of the EPO gene. Lodish Test., R. Trial Tr. at 1129. This, therefore, indicates that Amgen was *not* in *actual* possession of the entire scope of the invention at the time of filing; that is, that Amgen had not, at that time, itself demonstrated though experimentation the distant upstream placement of the promoter.

Although this evidence is compelling, when considered in light of prior case law and HMR/TKT's high burden of proof, it fails to persuade the Court that Amgen's specification is invalid for lack of written description. As discussed, the techniques disclosed in the specification are the same ones used in a process that places the promoter further upstream. Simply because further upstream placement was possible and applicants could have, as testified to by Dr. Lodish, done it and then described it in an example does not mean that the applicant must describe it. This is just the sort of argument rejected in *In re Vickers*, 141 F.2d 522, 988 (C.C.P.A. 1944). Although *In re Vickers* was a mechanical case, its reasoning applies here. If an inventor had to describe more than what he conceives is his best mode, most patents would be worth little. "The principle of the invention is a unit, and invariable;

the modes of its embodiment in a concrete invention may be numerous and in appearance very different from each other." *Id.* at 991 (quoting *Continental Bag Co. v. Eastern Paper Bag Co.*, 210 U.S. 405, 418 (1908)) (internal quotation marks omitted). Here, as explained above, the principal of the process was operative linkage—overcoming the natural restriction of the cell from making EPO by placing a strong promoter upstream of the EPO gene to be expressed and splicing out the intervening deleterious ATGs. Example 7 describes the best mode—the best process—and should not limit Amgen's right to exclude other processes that fall within the principal of the invention:

> The exclusive right to the thing patented is not secured, if the public are at liberty to make substantial copies of it, varying its form or proportions. And, therefore, the patentee, having described his invention, and shown its principles, and claimed it in that form which most perfectly embodies it, is, in contemplation of law, deemed to claim every form in which his invention may be copied, unless he manifests an intention to disclaim some of those forms.

In re Kirschbraun, 44 F.2d 675, 677 (C.C.P.A. 1930) (quoting *Winans* v. *Denmead*, 56 U.S. (15 How.) 330, 343 (1853)) (internal quotation marks omitted). Thus, Amgen's admission that Dr. Lin had not attempted to place the promoter further upstream is not dispositive. It does not show by clear and convincing evidence that the specification does not reasonable convey that the patentee was in possession but only that Dr. Lodish believed that Dr. Lin had not actually attempted one mode of the invention. Indeed, "patent law permits inventors to obtain patents based entirely on a written description of the invention, without actually constructing or selling the products embodying the invention." Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1681 n.69 (2003).

Moreover, this admission can be distinguished from the admission in *Gentry Gallery, Inc.* v. *Berkline Corp.*, upon which HMR/TKT relies for support. There, Gentry admitted he broadened his claims to cover placement of the controls outside the console only after competitors engaged in such placement. *Gentry*, 134 F.3d at 1479; *see also Amgen II*, 314 F.3d at 1334 (distinguishing the facts in *Gentry).* Further, in *Gentry*, the exact placement of the controls was clearly identified in the specification to be an essential element of the invention. *Gentry*, 134 F.3d at 1479. Here, there is absolutely no indication in the claims or the specification of a locational restriction. So while Dr. Lodish may have admitted that Amgen was not in literal possession of this embodiment of the invention at the time of filing, given the broadness of claims, this admission is not determinative. Judge Miller, as he did dissenting in *Application of Edwards*, would no doubt argue that this is in essence an admission that Amgen was not literally in possession of the invention as claimed since it did not ever even try to move the promoter further upstream. *See Edwards*, 568 F.2d at 1354-55. This Court concludes, however, that although the question is extremely close, Amgen was in possession of the invention as claimed, i.e., it used the words "operatively linked." The specification adequately describes what is claimed—a broad claim. A persuasive analogy is found in the enablement context. There, "[i]t is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention." *Amgen Inc.* v. *Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) [hereinafter *Chugai*] (citing *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976)), and *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) (discussing enablement of a publication under § 102 (b))).

Here, according to undisputed expert testimony, the specification communicates that in order to achieve "operative link[age]," what is important is placing a strong promoter

upstream of the ATG initiating codon of the EPO gene and splicing out unwanted ATGs. One skilled in the art who read Amgen's specification would understand that it is unimportant where upstream the promoter is pl. :ed, so long as it is genuinely "operatively linked." *Cf. Rasmussen*, 650 F.2d at 1214-15 (concluding that the generic step of "adheringly applying" one layer to an adjacent layer satisfied the written description requirement, because "one skilled in the art who read [the] specification would understand that it is unimportant how the layers are adhered, so long as they are adhered."); *Gentry*, 134 F.3d at 1480 (applying *Rasmussen* and considering what one skilled in the art would understand was important or essential to the invention). Amgen may claim other patentable means of operative linkage despite not having provided specific examples in its specification or a boilerplate statement that the examples in the specification were not meant to limit the breadth of the claims. *Rasmussen*, 650 F.2d at 1215; *cf. Kiruschbraun*, 44 F.2d at 677.[89] Thus, the phrase "operatively linked" appears to be supported by the specification.

In a nutshell, HMR/TKT misconstrues the focus of the section 112 inquiry, to wit, whether the claimed subject matter is adequately described, *see, e.g., Ralston-Purina Co.* v. *Far-Mar Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985); *In re Wilder*, 736 F.2d 1516, 1520 (Fed. Cir. 1984), and whether

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[89] HMR/TKT also relies on *PIN/NIP, Inc.* v. *Platte Chemical Co.*, 304 F.3d 1235 (Fed. Cir. 2002), to support its argument. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 48. The situation here, however, is distinguishable. In *PIN/NIP*, the Federal Circuit concluded that the broadened claims incorporated steps that were "quite distinct" from the original claims and what was actually described in the specification. 304 F.3d at 1247-48. None of the methods described in the specification were the same as the method in the broadened claim. *Id.* Here, as discussed above, the methods are the same and further upstream placement of the promoter is not directed to new subject matter different from that described in the patent.

the applicant asserted that he invented that which he did not, *Moba, B.V.* v. *Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). If the claims contained a limitation regarding promoter placement, HMR/TKT's arguments would have merit. They do not, and HMR/TKT points to nothing in the specification or prosecution history that justifies a location restriction for the promoter. Moreover, the specification adequately describes operative linkage and upstream promoter placement. Thus, HMR/TKT has failed to present clear and convincing evidence that Amgen failed adequately to describe the *claimed* inventions of the '698 and '349 patents.

b. Conclusion

Accordingly, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that the asserted claims of the '698 patent and claim 7 of the '349 patent are invalid for lack of written description under 35 U.S.C. § 112, ¶ 1.

C. Enablement

1. The '698 and '349 Patents

a. Discussion

A patent application must "contain a written description of the invention, and of the manner and process of making and using it . . . as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the same." 35 U.S.C. § 112, ¶ 1 (2000). "To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc.* v. *Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1461 (Fed. Cir. 1993)); *Plant Genetic Systems, H.V.* v. *Dekalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003) (same). The scope of the

claims must reasonably correlate to the scope of enablement provided by the specification to skilled artisans at the time of the patent's effective filing date. *Plant Genetic Systems*, 315 F.3d at 1340; *Hogan*, 559 F.2d at 604 (stating that enablement is determined as of the effective filing date of the patent). Therefore, crucial to the analysis is the state of the art at the time of the application—which is undisputedly 1983-84.

The parties' arguments for non-enablement run parallel to those regarding written description. Although the enablement requirement is separate and distinct from the written description requirement, the written description requirement is broader than the enablement requirement. *Vas-Cath*, 935 F.2d at 1563. Because the Court already held that the asserted claims of the '698 and '349 patents met the written description requirement based on the same arguments and evidence, it need address the enablement issue only briefly.

(1) HMR/TKT's First Argument: Endogenous DNA and Homologuous Recombination

HMR/TKT rightly claims that under the Court's claim construction, the asserted process claims of the '698 and '349 patents "do not enable one of skill in the art to produce EPO from vertebrate cells other than those transfected with exogenous cloned EPO DNA." HMR/TKT's Opening Br. After Trial at 48. As discussed above, however, it is undisputed that in 1983-84, endogenous activation technology and homologous recombination were not known to skilled artisans. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial at 34-35. As with the written description requirement, when considering enablement, later states of art cannot be employed as a basis for rejection. *Hogan*, 559 F.2d at 606; *Plant Genetics Systems*, 315 F.3d at 1340 (stating that *Hogan* held that "one could not use later-existing states of the art to invalidate a patent that was enabled for what it claimed at the time of filing"). Thus,

this argument fails with respect to the '349 and '698 patents. Moreover, because HMR/TKT makes no other enablement arguments with respect to claim 7 of the '349 patent, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that Claim 7 of the '349 patent was not enabled.

(2) HMR/TKT's Second Argument: Placement of the Promoter

HMR/TKT argues that Amgen's specification only enables operative linkage of promoter DNA and EPO DNA near or adjacent to the ATG initiation codon of a cloned and isolated EPO gene and that skilled artisans at the time would not have expected promoters placed further upstream to produce EPO. Furthermore, HMR/TKT contends that Amgen's argument—that enablement of one way to make a claimed product suffices—does not apply, because these are process claims not product claims. As a result, HMR/TKT argues, Amgen has forfeited its patent under 35 U.S.C. § 112, ¶ 1 by claiming all processes for making EPO but enabling only one.

HMR/TKT cites no cases that actually support its contention that process claims are somehow different than product claims when it comes to the enablement inquiry. HMR/TKT's Opening Br. After Trial at 49-50. The two cases that HMR/TKT does cite, *Genentech*, 108 F.3d at 1365[90] and *Enzo*

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[90] In *Genentech*, the patentee was "attempting to bootstrap a vague statement of a problem into an enabling disclosure sufficient to dominate someone else's solution of the problem." *Genentech*, 108 F.3d at 1365. This is not the case here. Amgen's specification does not provide "vague intimations of general ideas that may or may not be workable." *Id.* Instead, it provides guidance as to how operatively to link a promoter to EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA. It then provides an example of how this can be done. Moving the location of the promoter further upstream, as discussed above, requires the same methods disclosed in the specification along with an understanding of what actually existed further upstream.

Biochem, Inc. v. *Calgene, Inc.*, 188 F.3d 1362, 1371, 1374-75 (Fed. Cir. 1999),[91] stand only for the unremarkable proposition that a patent must teach those skilled in the art how to make and use the full scope of the invention. The Court holds that the '698 patent meets this requirement.

Here, HMR/TKT has not proved that the disclosure fails adequately to guide the skilled artisan to a process that places the promoter further upstream without undue experimentation. The thrust of HMR/TKT's argument—that the skilled worker would not have expected promoter linkages further upstream to produce EPO—has already been rejected by the Court. As discussed in the written description analysis, this Court finds as a factual matter that skilled artisans at the time of the application filing were aware of how to place promoters further upstream than is shown in example 7 of the '698 patent specification. Moreover, this Court found that all the techniques required to achieve such placement were taught in the specification. According to Dr. Lodish, using the specification, one skilled in the art could have placed a promoter further upstream and produced EPO. While he admitted that some problems might have occurred and that it would have taken a little bit of work, Lodish Test., Trial Tr. at 258, this does not necessarily equate to undue experimentation. *See In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That *some* experimentation may be required is not fatal; the issue

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This, according to Dr. Lodish and undisputed by HMR/TKT, could have been done in 1983-84 with a little bit of work, but was not done, because there was no reason to do it; that is, it would not have increased expression levels significantly.

[91] In *Enzo*, the Federal Circuit declared that the minimal disclosure constituted "no more than a plan or invitation to practice" the invention in cells other than E. coli. *Enzo*, 188 F.3d at 1374. Here, as will be discussed, Amgen provided reasonable detail to enable members of the public to understand and carry out the full scope of the invention without undue experimentation.

is whether the amount of experimentation required is 'undue.'" (quoting *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988))); *see also Wands*, 858 F.2d at 737 ("The key word is 'undue,' not 'experimentation.'" (quoting *Angstadt*, 537 F.2d at 504) (internal quotation marks omitted)). Thus, the evidence shows that all the methods required to conduct the process with the promoter further upstream were disclosed and one skilled in the art could replicate the invention using a further upstream promoter placement with some experimentation.

Tellingly, HMR/TKT has neither addressed in its memorandum nor pointed to record evidence regarding the amount of experimentation required by one of skill in the art to use the specification to place the promoter further upstream. Rather, it implicitly asks the Court to infer undue experimentation from general testimony about the development of the technology, the admission that Dr. Lin had not actually tried to place the promoter further upstream and did not know what was upstream of the EPO gene, and the absence of working examples disclosing placement of the promoter further upstream.[92] Given this lack of specific evidence, HMR/ TKT simply has not met its burden to prove undue experimentation. *See Moba*, 325 F.3d at 1321 (reaching a similar conclusion in the absence of specific evidence). First, the Court

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[92] HMR/TKT asserts in its Opening Brief after Trial that the reason that the skilled worker would not have expected that linkages further upstream would produce EPO is that "the expression process would be interrupted or misdirected by sequences, such as other start codons or stop codons, that intervened between the promoter and the EPO DNA." While this information about the difficulties of upstream promoter placement might work to support a finding of undue experimentation, HMR/TKT does not even argue that this is what it shows. Moreover, the only support it provides for this statement is the Court's previous finding in *Amgen I*, which was implicitly rejected by the Federal Circuit. Tellingly, HMR/TKT offers no concrete evidence or expert testimony addressing how it would have been difficult for the skilled artisan to make and use the invention as it is claimed or what type of experimentation would be necessary. *Id.* at 49.

points out that "it is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one of skill in the art to carry out the invention commensurate with the scope of his claims." *Chugai*, 927 F.2d at 1213 (citing *Angstadt*, 537 F.2d at 502); *Donohue*, 766 F.2d at 533 (discussing enablement of a publication under section 102(b) and concluding that "it is not . . . necessary that an invention disclosed . . . have actually been made in order to satisfy the enablement requirement[;] . . . the fact that [the inventor] did not attempt to make his disclosed invention does not indicate one way or the other whether the [patent] [is] enabling"). Second, the evidence produced at trial about the state of the art and the amount of guidance the specification provides suggest the contrary—that the patents at issue do teach those skilled in the art how to make and use the full scope of the invention. *Cf. Wands*, 858 F.2d at 737 (noting that the determination is not a "simple factual determination, but rather is a conclusion reached by weighing many factual considerations"). In light of the presumption of validity, HMR/TKT has failed to carry its burden with respect to this issue.

b. Conclusion

Accordingly, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that the process claims of the '349 and '698 patents were not enabled.

V. INFRINGEMENT

A. The '698 Patent: Claim 4-9

1. Background

At the close of Amgen's case-in-chief in the first trial, and before HMR/TKT had presented its case, this Court granted HMR/TKT's motions for judgments of non-infringement under Fed. R. Civ. P. 52(c), both literally and under the doctrine of equivalents of claims 4-9 of the '698 patent. *Amgen I*,

126 F. Supp. 2d at 99-101. In reaching this decision, the Court compared HMR/TKT's process to the specific embodiments exemplified in the '698 patent and found two significant differences between HMR/TKT's process and Amgen's process: (1) HMR/TKT's process uses homologous recombination to make its erythropoietin-producing cells and HRM/TKT's human EPO gene is endogenous to the human cell, whereas the preferred embodiment of the '698 patent employs heterologous recombination and uses human EPO DNA material that is exogenous; and (2) HMR/TKT's process uses cells in which the CMV promoter and enhancer are placed at a greater distance from the EPO DNA than did the particular examples found in the '698 patent, resulting in several ATG sites in HMR/TKT's process as opposed to only one in Amgen's examples. *Amgen I*, 126 F. Supp. 2d at 102-04. The Court considered these differences to be substantial ones and therefore held that Amgen had failed to show by a preponderance of the evidence that HMR/TKT's process infringes (literally or equivalently) the independent claims of the '698 patent. *Id.*

On appeal, the Federal Circuit vacated and remanded this Court's ruling regarding infringement of the '698 patent because the Court had erroneously compared the accused device to the preferred or commercial embodiments of the patent instead of to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1347. In the course of its ruling, the Federal Circuit made some specific statements about whether this Court's factual findings ought have any bearing on the infringement analysis when properly conducted. With regard to the Court's finding that HMR/TKT's process is homologous, the Federal Circuit pointed out that none of the claims at issue in the '698 patent contains any limitation regarding heterologous recombination. *Id.* Furthermore, the Federal Circuit pointed out this Court's claim construction—as opposed to a specific example in the specification—indicated that

HMR/TKT did infringe the "operatively linked" limitation in the claims.

As discussed briefly in the procedural history portion of this memorandum and order, the Court denied both Amgen's and HMR/TKT's renewed motions for summary judgment regarding infringement of the '698 patent [Doc. Nos. 664 and 665]. As a result, HMR/TKT presented its case on these issues at the remand trial.

HMR/TKT was also allowed to present its defense that it does not literally infringe claims 4-9 of the '698 patent under the reverse doctrine of equivalents. The Court decided to entertain such an argument because the facts that form the reverse doctrine of equivalents defense were always a part of HMR/TKT's interrogatory responses. In *Wright Medical Technology, Inc* v. *Osteonics Corp.*, 122 F.3d 1440, 1445 (Fed. Cir. 1997), the Federal Circuit remanded a case to the district court so it could determine the doctrine of equivalents issue even though the patentee had not argued equivalents, on the basis that the patentee had already introduced evidence in support of this argument. The analysis in *Wright*, although it addresses the doctrine of equivalents and not the reverse doctrine, is applicable here.[93] Therefore, the Court afforded

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[93] It is true that in *Texas Instruments Inc.* v. *United States International Trade Commission*, 988 F.2d 1165, 1176 (Fed. Cir. 1993) ("*Texas Instruments III*") the Federal Circuit refused to consider the alleged infringers' reverse doctrine of equivalents argument because it had not been raised before. *Id.* ("One does not make a reverse doctrine of equivalents argument simply by mounting a defense to literal or doctrine of equivalents infringement."). There, however, the prior proceeding was before the International Trade Commission, which had a strict rule regarding abandonment. In *Rolls-Royce Ltd.* v. *GTE Valeron Corp.*, 800 F.2d 1101, 1108 (Fed. Cir. 1986), however, the court implied that had the alleged infringer at least presented evidence regarding the doctrine of equivalents—even if not the reverse doctrine specifically—it may have entertained the reverse doctrine argument on appeal for the first time. *Id.* (rejecting alleged infringer's reverse doctrine of equivalents argument because there was "no

HMR/TKT the opportunity to present its defense and Amgen the opportunity to rebut.

2. The Claims at Issue

Claims 4 and 6 are the critical claims for resolving the infringement issue, as claims 5, 7, 8, and 9 are dependent.

Claim 4:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

'698 Patent, Ex. 1, col. 38: 37-47 (paragraph structure altered).

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evidence adduced at trial in support of a requested finding that the accused device was so far changed in principle that it performs in a substantially different way"); *cf. Brooktree Corp.* v. *Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1575 (Fed. Cir. 1992) ("[A]n appellate court may, in order to avoid injustice, elect to entertain arguments or consider issues raised for the first time on appeal."). This makes sense given the fact that the reverse doctrine was originally thought to be the application of the doctrine of equivalents in reverse. *See, e.g., Texas Instruments Inc.* v. *United States Int'l Trade Comm'n*, 846 F.2d 1369, 1371 (Fed. Cir. 1988) (*"Texas Instruments II"*) (referring to the reverse doctrine as the "doctrine of non-equivalents"); *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 608-609 (1950); *SRI Int'l* v. *Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1124-25 (Fed. Cir. 1985). For more information regarding the genesis of the reverse doctrine of equivalents see overview *infra*. The Court emphasizes that here the procedural posture is different than in these other cases. HMR/TKT here is pursuing this defense at the trial court level, as opposed to the appellate level, and had not presented its full case at the trial court level before the remand trial.

Claim 6:

> A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of: (a) growing under suitable nutrient conditions, vertebrate cells comprising amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and (b) isolating said glycoslated erythropoietin polypeptide expressed by said cells.

Id. at col. 38: 50-58 (paragraph structure altered).

3. Literal Infringement

a. Discussion

To determine whether an accused device literally infringes a patent claim, courts apply a two-step analysis. *See, e.g., Watts* v. *XL Sys., Inc.*, 232 F.3d 877, 880 (Fed. Cir. 2000); *Laitram Corp.* v. *Morehouse Indus., Inc.*, 143 F.3d 1456, 1461 (Fed. Cir. 1998). First, the court construes the claims to determine their scope as matter of law. *See Markman*, 517 U.S. at 370. Second, the court determines whether the claims cover the accused device. *See, e.g., Watts*, 232 F.3d at 880; *Cybor Corp.* v. *FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (en banc).

The only limitation of claims 4-9 of the '698 patent that HMR/TKT asserts it does not literally infringe is "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." *See, e.g.*, HMR/TKT's Reply Br. After Trial at 26-27; HMR/TKT's Opening Br. After Trial at 10-11. As discussed, *supra*, the Court conducted the first step of the inquiry and construed the term "DNA encoding" to mean "the genetic instructions for" the "mature erythropoietin amino acid sequence of FIG. 6." To conduct the second step, the Court must compare the properly construed claim with the

accused product to determine whether the accused product meets each and every limitation. *Bayer AG* v. *Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247-48 (Fed. Cir. 2000); *Young Dental Mfg. Co.* v. *Q3 Special Prods., Inc.*, 112 F.3d 1137, 1141 (Fed. Cir. 1997).

HMR/TKT argues that the claims require the genetic instructions for an EPO with the fully realized, secreted 166 amino acid sequence of Figure 6. *See* HMR/TKT's Reply Br. After Trial at 26-27; HMR/TKT's Opening Br. After Trial at 10-11. In support it points to the Court's ruling in *Amgen I*, in the context of the '080 patent, that the "mature erythropoietin amino acid sequence of FIG. 6" is "the fully realized form of the amino acid sequence of Figure 6," *Amgen I*, 126 F. Supp. 2d at 100, that is, one with a 166 amino acid sequence.

HMR/TKT's argument fails to persuade the Court because "the mature erythropoietin amino acid sequence of FIG 6" in the context of the '080 patent refers to the structure of the claimed glycoprotein whereas in the '698 claims it refers to the structure of a DNA in the claims.[94] This is not to suggest that the phrase should have different meanings in different contexts. Indeed, the parties agreed in *Amgen I* that the meaning of the term should be the same in both settings. *Amgen I*, 126 F. Supp. 2d at 86. Here, as in the context of the '080 patent, the phrase means the "fully realized form of the amino acid sequence of Figure 6." *Id.* at 87. In the '698 patent, however, the phrase is preceded by "DNA encoding," and thus the primary subject is the DNA whereas in the '080 patent the primary subject is the "erythropoietin glycoprotein" itself. See '080 and '698 Patents, Ex. 1. Although it is true that HMR 4396 is a glycoprotein containing 165 amino acids,

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[94] As Amgen points out (and HMR/TKT does not dispute), "DNA and protein are two distinct types of biological molecules," and, therefore, "the claim limitation must be carefully construed in light of the relevant claim language." Amgen's Reply to HMR/TKT's Findings of Fact at 36.

experts for both parties agree that HMR/TKT's R223 cells contain a DNA encoding EPO that "has the same codons for the same amino acids as is depicted in Dr. Lin's Figure 6." Kingston Test., R. Trial Tr. at 154: 21-155: 15; Lodish Test., Trial Tr. at 245: 16-247: 18; *id.* at 259: 12-15 (stating that HMR/TKT's R223 cells contain amplified DNA encoding the mature erythropoietin amino acid sequence of Figure 6); Lodish Test., R. Trial Tr. at 1066: 23-1067: 18.[95] In other words, each process encodes or provides the genetic instructions for the 1-166 amino acid sequence depicted in Figure 6, as each contains a DNA sequence having codons for amino acids +1 through +166 as depicted in Figure 6. As discussed in *Amgen I*, the reason that HMR/TKT claims an end-product that only has 165-amino acids while Amgen claims one that has 166 is that at the time Amgen's patents were written, it was not yet known that the last amino acid residue ultimately cleaves off prior to secretion of the EPO from the cell. *Amgen I*, 126 F. Supp. 2d at 86, 101.

HMR/TKT argues that "Amgen ignores that the 'cDNA' sequence it relies upon has a 'methionine, alanine, threonine' amino acid sequence, which is exon 1" and is derived from human growth hormone, not from EPO. HMR/TKT's Findings of Fact After Trial at 24, ¶ 104. This argument, however, is irrelevant. First, as Amgen points out—and HMR/TKT does not dispute—this argument involves the amino acids of

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[95] Dr. Lodish based his opinion on a comparison between the sequence of complementary DNA ("cDNA") made by HMR/TKT's contract manufacturer from the EPO DNA in R223 cells and the codons for amino acids at positions +1 to +166 of Figure 6. Lodish Test., R. Trial Tr. at 1066: 23-1067: 18; Lodish Test., Trial Tr. 245: 16-247: 18. It is undisputed that a cDNA is simply a DNA copy of a messenger RNA. In other words, the DNA is transcribed into an RNA transcript first. Then the RNA transcript is spliced into a messenger RNA. The cDNA is made as a direct DNA copy of the messenger RNA using reverse transcriptase so the sequence of the cDNA will be that of the messenger RNA. Lodish Test., R. Trial Tr. at 1066.

the leader sequence in HMR/TKT's R223 cells, yet the claims do not specifically address the leader sequence. Amgen's Reply to HMR/TKT's Findings of Fact at 36. The Court held, in *Amgen I*, that the mature EPO amino acid sequence of Figure 6 included only 166 amino acids, that is, positions +1 through +166. *Amgen I*, 126 F. Supp. 2d at 86, 100 (noting that Figure 6 depicts the amino acids starting from -27, the signal or leader peptide which is cleaved off, and concluding that in order for HMR 4396 to infringe literally, it "must contain an EPO glycoprotein comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids"). Consistent with this holding, Dr. Lodish testified at the remand trial that the amino acid sequence of the mature EPO in Figure 6 begins at the +1 position and ends at +166. Lodish Test., R. Trial Tr. at 1067: 5-18. Amgen's counsel suggested the same to Dr. Kingston, and he never contradicted this implication. Kingston Test., R. Trial Tr. at 156: 14-23 (agreeing with Amgen's counsel's depiction of Figure 6 as having codons for a leader sequence and then codons for the "mature sequence" beginning at +1). Second, this argument ignores expert testimony proffered by both parties, noted above, that HMR/TKT's R223 contain DNA encoding the mature erythropoietin amino acid sequence of Figure 6, as defined by this Court, regardless of any differences in the leader sequences.

Even so, HMR/TKT argues that proof that its DNA is the same as Amgen's DNA is not enough. It contends that the claims require production of an EPO product with 166 amino acids because "the mature erythropoietin amino acid sequence of Fig. 6" is followed in the claims by a clause which states "said glycosylated erythropoietin polypeptide" is "isolated." HMR/TKT's Opening Br. After Trial at 11.

Based on the language of the claims, including the preambles, the Court rejects this argument and concludes that "the mature erythropoietin amino acid sequence of FIG. 6"

modifies the words "DNA encoding" in the cells grown in step (a)—and does not modify "glycosylatd erythropoietin polypeptide" isolated in step (b). This interpretation is supported by evidence, proffered by Amgen and undisputed by HMR/TKT, that the proper antecedent basis is provided only by use of prior *identical* language in the claim. See Manual of Patent Examining Procedure 2173.05(e) (6th ed. 1997); Amgen's Reply to HMR/TKT's Findings of Fact at 37. Here, "glycosylated erythropoietin polypeptide" is previously found only in the preamble and not in part (a) of the claim.[96] Part (a), although it refers to the "mature erythropoietin amino acid sequence of Fig. 6," concerns the DNA that is doing the encoding—not the EPO itself. Part (b) merely addresses the next step in the process which is the step of isolating. Thus, "said glycosylated erythropoietin polypeptide" refers back to the preamble before steps (a) and (b) are described. This is the only reading that makes grammatical sense. Moreover, it is consistent with how the claims of the '080 patent are read. There, "said erythropoietin glycoprotein" always refers back to the exact identical language at the beginning of the claim and not to the attributes of the glycoprotein itself. '080 Patent, Ex. 1, col. 38: 39-50.

b. Conclusion

In sum, Amgen has shown by a preponderance of the evidence that HMR/TKT's HMR 4396 does indeed literally infringe claims 4-9 of the '698 patent. Before ruling that Amgen prevails on this issue, however, the Court must address HMR/TKT's reverse doctrine of equivalents defense.

[96] HMR/TKT neither claims nor cites to any authority claiming that the antecedent for a claim limitation must be found in the meat of the claim and not in the preamble.

4. Reverse Doctrine of Equivalents

a. Overview of the Doctrine

The reverse doctrine of equivalents is an equitable doctrine that a court applies when it finds that the accused device literally infringes a patented invention, but is so fundamentally different from the patented invention that a judgment of infringement would be inappropriate. *Texas Instruments, Inc.* v. *United States International Trade Commission*, 846 F.2d 1369, 1371 (Fed. Cir. 1988) (*"Texas Instruments II"*) (noting that it might be better described as "the doctrine of non-equivalents"); *Scripps Clinic & Research Found.* v. *Genentech Inc.*, 927 F.2d 1565, 1581 (Fed. Cir. 1991). The doctrine was first articulated by the Supreme Court in *Boyden Power-Brake Co.* v. *Westinghouse*, 170 U.S. 537, 568 (1898) (establishing that the doctrine of equivalents could be used defensively); *Gillette* v. *S.C. Johnson & Son, Inc.*, Nos. 83-2657-N, 83-3201-N, 1989 WL 87374, at *19 (D. Mass. July 31, 1989) (Collings, M.J.) (commenting that *Westinghouse* was the seminal case respecting the reverse doctrine of equivalents); George M. Sirilla, Thomas P. Feddo & Michael C. Antone, *The Doctrine of Equivalents: Both a Sword and a Shield*, 13 Fed. Cir. B.J. 75, 77-78 (2003) (noting that *Westinghouse* was a "seminal case" in establishing the use of the doctrine of equivalents as a shield); John F. Duffy, *The Festo Decision and the Return of the Supreme Court to the Bar of Patents*, 2002 Sup. Ct. Rev. 273, 315 (2002). Approximately fifty years later, in *Graver Tank & Mfg. Co.* v. *Linde Air Products Co.*, 339 U.S. 605, 608-609 (1950), the Supreme Court explicitly endorsed the reverse doctrine of equivalents. *Graver Tank*, 339 U.S. at 608-609 (noting that the doctrine of equivalents "is not always applied in favor of the patentee but is sometimes used against him" when "the invention is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way"); *Scripps*, 927 F.2d at 1581 (quoting *Graver Tank*);

Tate Access Floors, Inc. v. *Interface Architectural Res. Inc.*, 279 F.3d 1357, 1368 (Fed. Cir. 2002) (remarking that the Supreme Court referred to the reverse doctrine in *Graver Tank*).

The reverse doctrine of equivalents is applied equitably based upon factual determinations made after "the accused infringer proves that, despite the asserted claims literally reading on the accused devise, 'it has been so changed that it is no longer the same invention.'" *Amgen II*, 314 F. 3d at 1351 (quoting *Del Mar Avionics, Inc.* v. *Quinton Instrument Co.*, 836 F.2d 1320, 1325 (Fed. Cir. 1987)).[97] As the Supreme Court explained in *Westinghouse:*

> The patentee may bring the defendant within the letter of his claims, but if the latter has so far changed the principle of the device that the claims of the patent, literally construed, have ceased to represent his actual invention, he is as little subject to be adjudged an in-

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[97] The Federal Circuit made clear in *SRI International*, that after the patentee has proved literal infringement, "*the accused infringer* may undertake the burden of going forward to establish the fact of non-infringement under the reverse doctrine of equivalents." 775 F.2d at 1123-24 (emphasis added). It is only *after* the alleged infringer makes a prima facie showing that its process is so far changed in principle from the claimed processes that the patentee, "who retains the burden of persuasion on infringement," must rebut. *Id.* at 1124; *see also SmithKline Diagnostics, Inc.* v. *Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988) (observing that the infringement inquiry does not necessarily end when claims read literally on the accused product because the accused "may establish the fact of non-infringement by carrying its burden of going forward to show its device 'has been so far changed in principle that it performs the same or similar function in a substantially different way'" (quoting *SRI International*, 775 F.2d at 1123-24)).

Thus, here—notwithstanding its unpersuasive arguments to the contrary—HMR/TKT has the burden of making a prima facie showing that "the accused device is outside the fair and equitable scope of the invention." Sirilla, Feddo & Antone, *supra*, at 101.

> fringer as one who has violated the letter of a statute has to be convicted, when he has done nothing in conflict with its spirit and intent.

170 U.S. at 568. Thus, the determination of whether the reverse doctrine should apply is not made in a vacuum. *Graver Tank*, 339 U.S. at 609; *Amgen II*, 314 F.3d at 1351. Nor is it made by merely considering the language of the claims themselves.[98]

Rather, the Court must determine the originally intended scope, the "spirit and intent" of the claims, *Westinghouse*, 170 U.S. at 568, based on the "the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank*, 339 U.S. at 609; *see also Texas Instruments II*, 846 F.2d at 1372 (explaining that the reverse doctrine concerns the "original intended scope" of the claims); *Scripps*, 927 F.2d at 1581 ("[T]he purpose of the 'reverse' doctrine is to prevent unwarranted extension of the claims beyond a *fair* scope of the patentee's invention." (emphasis added)). In other words, "the analysis requires a determination of the 'substance of the invention,' the 'thing' or 'article' patented, or 'the principle of the device.'" Sirilla, Feddo & Antone, *supra*, at 83 (citing *Festo II*, 535 U.S. at 731, *Westinghouse*, 170 U.S. at 568, and *Winans*, 56 U.S. at 343).

Although the Federal Circuit recognizes this doctrine, it is rarely invoked successfully. Shyh-Jen Wang & Shyh-Yau Wang, *The Verification Flow Chart of Patent Infringement*, 86 J. Pat. & Trademark Off. Soc'y 74, 78 (2004) ("[I]t is not often raised and even less frequently successful."); Burk & Lemley, *supra*, at 1657. Indeed, according to the Federal Circuit, it has never upheld a decision of non-infringement based on the reverse doctrine of equivalents. *Tate*, 279 F.3d at

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[98] If it were based solely on the claim language itself, the analysis would not differ from basic literal infringement and section 112 analysis.

1368 (labeling the reverse doctrine "anachronistic").[99] This may be because circumstances in which the doctrine is satisfied are very rare. *See, e.g., SRI Int'l*, 775 F.2d at 1124, n.19 ("Because products on which patent claims are readable word for word often are in fact the same, perform the same function in the same way, and achieve the same result, as the claimed invention, a defense based on the reverse doctrine of equivalents is rarely offered."); *Caterpillar Tractor Co.* v. *Berco, S.P.A.*, 714 F.2d 1110, 1115, n.3 (Fed. Cir. 1983) ("It is possible, of course, for a claim to be literally but not actually infringed, where, for example, a claim may 'read on' a structure having no relation to the invention. Instances are rare."); Donald S. Chisum, *Chisum on Patents*, § 18.04 (4) (b) at 18-392 (2000).[100] On the other hand, its rarity may be, as the

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[99] Although the Federal Circuit may never have upheld a decision based on the reverse doctrine of equivalents, some appellate courts, before the Federal Circuit was created, applied the doctrine of equivalents defensively without expressly identifying it as the reverse doctrine. *See, e.g., Leesona Corp.* v. *United States*, 530 F.2d 896, 906 (Ct. Cl. 1986); *Foster Cathead Co.* v. *Hasha*, 382 F.2d 761, 765 (5th Cir. 1967); *see also* Sirilla, Feddo & Antone, *supra*, at 86-87 (commenting on these decisions and concluding that each implicitly applied the reverse doctrine of equivalents).

[100] District Courts also appear to be reluctant to apply the reverse doctrine of equivalents. *But see Marvin Glass & Assocs.* v. *Sears, Roebuck & Co.*, 318 F. Supp. 1089, 1104-5 (S.D. Tex. 1970). Although the reverse doctrine is recognized, it is often deemed inapplicable, or the court finds that there is insufficient evidence to support application of the doctrine. *See, e.g., SDS USA Inc.* v. *Ken Specialties, Inc.*, 122 F. Supp. 2d 533, 541 (D. N.J. 2000); *cf. Monsanto Co.* v. *Mycogen Plant Science, Inc.*, 61 F. Supp. 2d 133, 188 (D. Del. 1999) (entering judgement as matter of law, holding that the jury acted unreasonably in finding non-infringement based on reverse doctrine of equivalents). There are instances, however, where district courts have based a finding of non-infringement on the reverse doctrine of equivalents or used it as an alternative ground for their decision. *See, e.g., Precision Metal Fabricators* v. *Jetstream Sys.*, 693 F. Supp. 814, 819 (N.D. Cal. 1988) (granting summary judgment in favor of defendants based on the reverse doctrine of equivalents); *Brenner* v. *Rec-*

Federal Circuit suggested in *Tate*, a result of the enactment of 35 U.S.C. § 112. *Tate*, 279 F.3d at 1368 (explaining that "the written description requirements of 35 U.S.C. § 112 are co-extensive with the broadest possible reach of the reverse doctrine of equivalents"); Joseph Yang & Roxana H. Yang, *An Update on the Doctrine of Equivalents—Where Do We Stand in 2003?*, 749 Practicing L. Inst. 521, 561 (2003) (concluding that this is a dead doctrine due to the enactment of section 112). In other words, alleged infringers that perhaps could successfully have evoked the reverse doctrine of equivalents do not attempt to do so because they prevail with section 112 challenges on grounds such as inadequate written description, lack of enablement, or means-plus-function. *See, e.g.*, *Texas Instruments, Inc.* v. *United States Int'l Trade Comm'n*, 805 F.2d 1558, 1571-2 (Fed. Cir. 1986) ("*Texas Instruments I*") (applying the principles underlying the reverse doctrine of equivalents in the context of section 112, paragraph 6). As the Federal Circuit explained in *Texas Instruments II*, 846 F.2d at 1372, section 112 and the reverse doctrine are intertwined:

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ognition Equip. Inc., 593 F. Supp. 1275, 1278 (S.D.N.Y. 1984) (invoking the reverse doctrine of equivalents as an alternative ground for non-infringement); *SmithKline Diagnostics, Inc.* v. *Helena Labs., Inc.*, 662 F. Supp. 622, 628 (E.D. Tex. 1987) (same); *Technicon Instruments Corp.* v. *Alpkem Corp.*, 664 F. Supp. 1558, 1575 (D. Or. 1986). It appears, however, that the District Court of Massachusetts has never held non-infringement based on the reverse doctrine of equivalents. *VLT, Inc.* v. *Power-One, Inc.*, No. 01-CV-10207, 2003 WL 43364 (D. Mass. Jan. 3, 2003) (Saris, J.) (concluding that the court need not address the reverse doctrine of equivalents because the court rejected the proposed claim construction); *Amgen, Inc.* v. *Chugai Pharmaceuticals Co., Ltd.*, Civ.A. No. 87-2617-Y, 1989 WL 169006, at *85 (D. Mass., Dec. 11, 1989) (Saris, J.) (explaining that defendants should request reconsideration by this Court if they want to raise the issue); *Gillette* v. *S.C. Johnson & Son, Inc.*, Nos. 83-2657-N, 83-3201-N, 1989 WL 87374, at *19 (D. Mass. July 31, 1989) (Collings, M.J.).

> The reverse doctrine of equivalents is invoked when claims are written more broadly than the disclosure warrants. The purpose of restricting the scope of such claims is not only to avoid a holding of infringement when a court deems it appropriate, but often is to preserve the validity of the claims with respect to their original intended scope.

846 F.2d 1369, 1372.[101]

Despite the paucity of cases relying on the reverse doctrine, the doctrine is not yet dead.[102] Indeed, just last year, the Federal Circuit implied in two separate cases that the reverse doctrine of equivalents still had a heart beat, albeit a faint one. *See Amgen II*, 314 F.3d at 1351 (discussing the doctrine as though it were a viable one, but holding that it did not apply to the case at bar); *Plant Genetic Systems, N.V.* v. *Dekalb Genetics Corp.*, 315 F.3d 1335, 1341 (Fed. Cir. 2003) ("[T]he judicially-developed 'reverse doctrine of equivalents,' requiring interpretation of claims in light of the specification, may be safely relied upon to preclude *improper* enforcement against later developers."); Burk & Lemley, *supra*, at 1657, n.308 (interpreting *Amgen II* as implying the viability of the reverse doctrine). This is rightly so.

Although both the reverse doctrine of equivalents and section 112 spring from the same roots and very often take

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[101] If the claims are broader than the "spirit and intent" of the invention, this will most likely be apparent by a close reading of the specification. At this point, a section 112 challenge may be initiated in lieu of a reverse doctrine of equivalents argument. As discussed immediately *infra*, however, this challenge may not always be successful. This is where the reverse doctrine of equivalents comes in.

[102] Despite not relying on it, the Federal Circuit has affirmed the viability of the reverse doctrine of equivalents many times, *see, e.g.*, Sirilla, Feddo & Antone, *supra*, at 87-97 and app. A (identifying many cases that applied the principals of the reverse doctrine and that supported its viability).

account of the same factors and considerations," *Texas Instruments II*, 846 F.2d at 1372 (Davis, J., concurring),[103] the reverse doctrine is theoretically—if not practically—distinct from section 112 requirements. *See, e.g.*, *Warner-Jenkinson Co, Inc.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17, 35 (1997) (rejecting the notion expressed in *Tate* that section 112 nullified or codified the reverse doctrine); *cf.* Sirilla, Feddo & Antone, *supra*, at 82, 102 (stating that the requirements of section 112 provide the context in deciding the rightful reach of the claims and thereby implying that section 112 and the reverse doctrine are distinct); Ronald D. Hantman, *Why Not the Statute?: Revisited*, 83 J. Pat. & Trademark Off. Soc'y 685, 704 (2001) (noting that "the Federal Circuit has interpreted the reverse doctrine of equivalents as distinct from section 112" but opining that they are not). The reverse doctrine of equivalents, unlike the requirements of section 112, supports innovation—especially in the area of biotechnology where blocking patents are common—because it offers some chance of protection to those that make substantial changes or radical improvements to inventions. Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 Tex. L. Rev. 989, 991, 1011, 1067 (1997) ("*Economics*") ("The application of the reverse doctrine is to protect substantial improvers from infringing if they are sufficiently radical."); *cf.* Burk & Lemley, *supra*, at 1681; Mark R. Patterson, *Inventions, Industry Standards, and Intellectual Property*, 17 Berkeley Tech. L.J. 1043, 1052 (2002) ("The reverse doctrine of equivalents can be viewed as a means of

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[103] Indeed, many scholars and judges have noted the similarity in operation between applying section 112, ¶ 6 and the reverse doctrine of equivalents. Both restrict the coverage of literal claim language. *See, e.g.*, *Valmont* v. *Reinke*, 983 F.2d 1039, 1042 (Fed. Cir. 1993); *Johnston* v. *IVAC Corp.*, 885 F.2d 1574, 1580 (Fed. Cir. 1989); *see generally* Gary M. Butter, Marta E. Delsignore, Kimberly J. McGraw & Louis S. Sorell, *Selected Aspects of the Impact of Patent Prosecution on Patent Litigation Issues*, 750 Practicing L. Inst. 317 (2003).

avoiding hold-ups that can deter innovation."); *see also* Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 Colum. L. Rev. 839, 866 (1990) ("[T]he reverse doctrine of equivalents solves the problem of [hold-up by blocking patents] by, in effect, excusing the improver from infringement liability—and therefore removing the original patentee's hold-up right.").[104] As the Federal Circuit explained in *Plant Genetics*, should an alleged infringer lose its section 112 arguments because the technology was new and therefore did not need to be described or enabled, it can bring a challenge under the reverse doctrine of equivalents. *Plant Genetics*, 315 F.3d at 1341. Thus, the reverse doctrine, unlike section 112, acts as a "judicial safety valve," Robert Merges, *Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents*, 62 Tenn. L. Rev. 75, 75-76 (1994) ("*Blocking Patents*"), allowing consideration of equity and fairness, "soft factors," that a section 112 inquiry does not incorporate.[105] In essence, the reverse doctrine, when equity demands it, re-verses the protection given to broad patents that satisfy section 112. *Cf.* Lemley, *Economics*, at 1003 (noting that patent owners are not limited to what they actually discovered "so long as the

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[104] A blocking patent situation occurs when an improvement is patented but the improvement patent infringes on the original patent. Lemley, *Economics*, at 1009-1010. The original patent owner is entitled to damages from past infringement and an injunction against future use of the infringing invention. *Id.* At the same time, however, the original patent owner cannot use the patented improvement without risking liability for damages and a potential injunction. *Id.* Thus, "the original patent owner can prevent the improver from using his patented technology but the improver can prevent the original patent owner from using the improvement. Unless the parties bargain, no one gets the benefit of the improvement." *Id.*

[105] Merges argues that it should be used by judges to "releas[e] pressure that builds up when pioneers and improvers fail to agree to a license." Merges, *Blocking Patents*, at 75-76.

patentee describes the general class and its characteristics with sufficient precision that others can identify and use them without undue experimentation"); *cf.* Antony L. Ryan & Roger G. Brooks, *Innovation vs. Evasion: Clarifying Patent Rights in Second Generation Genes and Proteins*, 17 Berkeley Tech. L.J. 1265, 1280 (2002) (noting that "in theory the reverse doctrine of equivalents" could provide some relief in the biotech arena where innovation is stifled by broad patents but concluding that it is applied so rarely that its comfort is slight); Toshiko Takenaka, *Doctrine of Equivalents After* Hilton *Davis: A Comparative Law Analysis*, 22 Rutgers Computer & Tech. L.J. 479, 506-07 (1996) ("Application of the reverse doctrine of equivalents may prevent enforcing the patent as broadly as drafted.").

This is not to suggest that the reverse doctrine of equivalents should be invoked frequently. To the contrary, it should be saved—and apparently is—for the inventor that *radically*, not just modestly, improves upon the prior art such that there is a "manifest departure from the principle in the [patentee's] patent." *Westinghouse*, 170 U.S. at 572, 579 (commenting that the alleged infringer's invention did not infringe not just because it was novel or changed in principle but because it solved an important problem that the patentee's invention did not and pointing out that the alleged infringer's invention was a "radical departure");[106] *see generally SRI International*, 775 F.2d at 1123 (emphasizing that the reverse doctrine protects when the alleged infringer's device is "so *far* changed in principle that it performs in a *substantially different* way"

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[106] In *Westinghouse*, the device described by the original patentee could not produce the result achieved by the accused device, that is, it could not quickly and smoothly stop a moving train. *Westinghouse*, 170 U.S. at 571-72. The Supreme Court held that the alleged infringer's way of accomplishing the function of the patent, applying brakes to a moving train, was such a "radical departure," *id.* at 579, and "so different" that infringement could not be found. *Id.* at 723-24.

(internal quotation marks omitted)); *Scripps*, 927 F.2d at 1581 (suggesting application of the reverse doctrine on remand where the defendant produced similar biological materials by a potentially radically new biotechnological process); *cf. Winans*, 56 U.S. at 342-343 ("It is only *ingenious* diversities of form and proportion, presenting the appearance of something unlike the thing patented," which indicate that infringement should not be found. (emphasis added)); *see also Diamond Int'l Corp.* v. *Maryland Fresh Eggs, Inc.*, 374 F. Supp. 1223, 1247 (D. Md. 1974) (noting that it is the "really meritorious improver" who deserves the benefit of the concept of the reverse doctrine of equivalents), *rev'd on other grounds*, 523 F.2d 113 (4th Cir.); Lemley, *Economics*, at 1067; Merges, *Blocking Patents*, at 92-94 (opining that the alleged infringer must show a "radical improvement" or "significant contribution" or "substantial technological improvement" such as that shown in *Westinghouse* or *Scripps*); Donna M. Gitter, *International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U. L.R. 1623, n.411 (2001); Sean Hogle, *Unauthorized Derivative Source Code*, 18 No. 5 Computer & Internet Law. 1, 3 (2001). Only then will the certainty of patent law be preserved while still encouraging and rewarding substantial, radical, innovation. Merges & Nelson, *supra*, at 867 n.120; *cf.* Merges, *Blocking Patents*, at 92 (asserting that the reverse doctrine creates enough of a threat to pioneer patentees to positively influence the changes of a society productive agreement between the pioneer and radical improver); Lemley, *Economics*, at 1012 ("The reverse doctrine of equivalents therefore benefits radical improvers at the expense of the original patentee, and so encourages radical improvements, just as the blocking patents rule provides some lesser encouragement to significant improvements.").

b. Discussion

HMR/TKT argues that it does not infringe claims 4-9 of the '698 patent because its process is "so far removed in terms of its principles of operation from the process Amgen disclosed." HMR/TKT's Opening Br. After Trial at 18. Although HMR/TKT proffers many reasons in support of its position, it has failed to make out a prima facie case.[107] As Amgen aptly points out, HMR/TKT makes the same mistake with each of its arguments. It repeatedly compares its process to the examples disclosed in Amgen's patent specification instead of to the "equitable scope of the claims." *Scripps*, 927 F.2d at 1581 ("Application of the doctrine requires that facts specific to the accused device be determined and weighed against the equitable scope of the claims, which in turn is determined in light of the specification, the prosecution history, and the prior art."); *cf. Amgen II*, 314 F.3d at 1351 (rejecting HMR/TKT's reverse doctrine of equivalents arguments regarding the '349 patent that compared its invention to the examples in the specification and not to the claims); *SDS USA, Inc.* v. *Ken Specialties, Inc.*, 122 F. Supp. 2d 533, 541 (D.N.J. 2000) (holding that the accused infringer had "fail[ed] to mount a prima facie case because it [had] compare[d] the accused product not to the . . . patent, but to [the patentee's] commercial embodiment"). The proper question, however, is how any purported differences are changed in principle from Amgen's patented processes given "the context of the patent, the prior art, and the particular circumstances of the case." *Graver Tank*, 339 U.S. at 609; *United States Steel Corp.*, 865 F.2d at 1253 n.9. (affirming district court's decision that was based on the principle of the contribution made by the inventor); *Scripps*, 927 F.2d at 1581. Thus, as will be explained below, although HMR/TKT

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[107] Even if HMR/TKT had made out a prima facie case, Amgen has successfully rebutted the defense, as will be made clear in the discussion below.

presents evidence showing many differences between its process and those specifically exemplified in Amgen's specification, it fails to prove that these differences matter.[108]

(1) Homologous Recombination, Endogenous EPO DNA, and The Neighborhood's Effect on the Production of EPO

(a) Homologous Recombination and Endogenous EPO DNA[109]

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[108] HMR/TKT groups and labels its reasons for applying the reverse doctrine of equivalents differently in its various submissions. *See, e.g.*, HMR/TKT's Opening Br. After Trial 11-19; HMR/TKT's Proposed Findings of Fact at 25-41. For ease of analysis, based on the parties' arguments at trial and submissions after trial, and the overlap among the arguments, the Court groups HMR/TKT's reasons into four areas. While the Court has considered each of HMR/TKT's contentions, and concluded that each fails for the primary reasons explained above, not every contention need be addressed specifically in this section.

[109] The Court first addresses homologous recombination and endogenous EPO DNA because HMR/TKT seems to assert that these points, in their own right—aside from the neighborhood theory—work to justify evocation of the reverse doctrine of equivalents. HMR/TKT's reliance on these differences appears to stem from the Court's prior factual findings and legal conclusions. Indeed, the Court previously found that HMR/TKT did not equivalently infringe the '698 patent because HMR/TKT's process performs the same function in a substantially different way, based, in part, on the fact that HMR used homologous recombination and endogenous EPO DNA while the embodiments in Amgen's specification only addressed heterologous recombination and exogenous EPO DNA. *Amgen I*, 126 F. Supp. 2d at 102-04. As discussed earlier, however, the Federal Circuit held this comparison between HMR/TKT's process and the embodiments in Amgen's specification to be erroneous. *Amgen II*, 314 F.3d at 1347. While it is true that "equivalence and non-equivalence, . . . are but opposites of the same coin," *Sri Int'l*, 775 F.2d at 1124-25, candidly, the Court in *Amgen I* did not conduct the proper equivalents analysis. Moreover, it did not, in making its prior determination, consider the intended scope of the claims or the principles of the invention—key components of any reverse doctrine of equivalents analysis. In short, the Court's prior equivalence determination was not based on the correct or

HMR/TKT repeatedly asserts that (1) its process is different because it uses homologous recombination (as opposed to heterologous recombination); and (2) its EPO gene is different in structure because HMR/TKT's EPO DNA is endogenous and Amgen's is exogenous. HMR/TKT's Opening Br. After Trial at 13; HMR/TKT's Proposed Findings of Fact ¶ 141; HMR/TKT's Reply Br. After Trial at 28.[110]

Tellingly, aside from the neighborhood theory (discussed immediately below), HMR/TKT does not even attempt to explain how these differences matter—that is, how they are different in principle from the processes disclosed in Amgen's patents. Instead, it primarily relies on this Court's prior findings, in the equivalent infringement context, that HMR/TKT's process is not substantially similar to Amgen's because, *inter alia*, it uses homologous recombination and

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complete set of factors upon which a determination regarding equivalents should be made. Therefore, the Court's prior holding that HMR/TKT's process performs the same function in a substantially different way is simply irrelevant to this analysis here.

[110] As discussed earlier, it is undisputed that endogenous activation technology and homologous recombination were unknown to those skilled in the art when Amgen filed its patent application in 1983-84. HMR/TKT's Findings of Fact ¶ 488; Amgen's Reply to HMR/TKT's Opening Br. After Trial [Doc. No. 815] at 34-35. As a result, exogenous EPO DNA expression systems and heterologous recombination techniques were not depicted in Amgen's examples in the patent. Trial Tr. at 375: 19-25; 376-381; *see also Amgen I*, 126 F. Supp. 2d at 102. For example, Amgen's patent describes transfecting Chinese Hamster Ovary ("CHO") cells with a vector that contains both viral promoter DNA and the human EPO gene. '933 Patent, Ex. 1, col. 25: 55-61; Trial Tr. at 174: 18-22, 1330: 2-5. Thus, the human EPO DNA material is exogenous to the hamster host cell. *Id.*; *Amgen I*, 126 F. Supp. 2d at 102. HMR/TKT, on the other hand, employs homologous recombination. *Id.* HMR/TKT does not utilize a host cell from a non-human species; rather, it manipulates the human EPO gene where it naturally resides in an HT1080 human cell line. Trial Tr. at 165: 21. The human EPO gene, therefore, is endogenous to the human cell as opposed to exogenous.

endogenous activation techniques. *See, e.g., Amgen I*, 126 F. Supp. 2d at 102-03 (concluding that "[HMR/]TKT is able to express high levels of human EPO in human cells without having to rely upon host cells from alternative species"). While it is true that the Court in *Amgen I* asserted that use of endogenous DNA was "an important distinction" in its eyes, the Court's vantage point has now changed. The Federal Circuit has made clear that the proper infringement analysis—of which the reverse doctrine of equivalents is a part—requires the Court to look at the properly construed claims and not to limit its purview to the invention as described in embodiments in the specification. *See Amgen II*, 314 F.3d at 1351 (making clear that the claims must frame the analysis when considering the reverse doctrine of equivalents). Clearly, endogenous DNA and homologous recombination are not explicated in any claim limitations. Moreover, the Court has already found—and the Federal Circuit upheld—that the specification does not limit the claims to exogenous activation and homogenous recombination. *Id.* Thus, the mere fact that HMR/TKT utilizes these other techniques does not alone demonstrate any substantial change from Amgen's patents. As the Court found in *Amgen I* in the context of the '349 patent, whether DNA encoding human EPO originated within or outside of the host cell simply does not matter, because the coding sequences of the DNA are the same and both DNA sequences function the same way to produce human EPO. 126 F. Supp. 2d at 121; *see also* Lodish Test., R. Trial Tr. at 1098: 6-12.

True, heterologous recombination and endogenous activation techniques were not known by skilled artisans at the time Amgen filed its application. Equivalent infringement, however, is evaluated based on the date of infringement. *Warner-Jenkinson*, 520 U.S. at 37. Here, the evidence does not show that these techniques are different in principle than those espoused in Amgen's patent. Moreover, the mere use of new technology—even when it is superior—does not on its own

justify the application of the reverse doctrine of equivalents. *Westinghouse*, 170 U.S. at 723 (noting that infringement can be found even if the device is an improvement upon that of the patentee); *Studiengesellschaft Kohle, m.b.H.* v. *Dart Indus., Inc.*, 726 F.2d 724, 728 (Fed. Cir. 1984) ("That [the alleged infringer's] catalysts may be superior to those actually invented, disclosed, and contemplated by [the patentee] would not by itself remove [the alleged infringer's] catalysts from the scope of [the patentee's] claims."); *Phillips Petroleum Co.* v. *United States Steel Corp.*, 673 F. Supp. 1278, 1357 (D. Del. 1987) (similar); Lemley, *Economics*, at 1010-11 (noting that "any invention, no matter how pioneering, can be thought of as an improvement on prior work," and that "not all improvements escape infringement," even significant ones, but that "radical improvements are protected under the reverse doctrine of equivalents"). HMR/TKT must somehow show its product or process is changed "in principle" from what is embraced in the patent claims—that is, that these differences "amount to a significant contribution that takes the invention outside the equitable bounds of the patent." *Westinghouse*, 170 U.S. at 572, 579 (noting that it was not just novel but also a substantial improvement); *cf. Scripps*, 927 F.2d at 1581; Merges & Nelson, *supra*, at 864-65 (interpreting the reverse doctrine as requiring not just novelty but a significant contribution or substantial improvement and relying on *Westinghouse* and *SRI International* as support). Importantly, HMR/TKT provides no support—aside from this Court's dicta—that its endogenous activation technique or homologous recombination was an improvement "so radical that it fundamentally changed the nature of the invention." Lemley, *Economics*, at 1067. HMR/TKT merely points to differences such as "endogenous genes in mammalian cells have a methylation pattern that exogenous genes lack." HMR/TKT's Proposed Findings of Fact ¶ 141. Aside from the neighborhood theory, discussed and rejected by the Court

below, HMR/TKT does not explain how these differences matter. Its showing is simply inadequate.

(b) The Endogenous EPO Neighborhood and Its Effect on EPO Production

HMR/TKT argues that how the gene construct "functions with the surrounding neighborhood to produce EPO is completely different in HMR/TKT's and Amgen's cells." HMR/TKT's Proposed Findings of Fact at 29-32; HMR/TKT's Opening Br. After Trial at 16 (claiming that the way in which expression of human EPO is accomplished is significantly different in HMR/TKT's process). In support, it explains that HMR/TKT activates the normally silent EPO gene and inserts it amidst the endogenous EPO neighborhood. HMR/TKT's Proposed Findings of Fact ¶¶ 122-125. This, according to HMR/TKT, enables the promoter "to work with other nearby enhancers and the EPO gene neighborhood to contribute to the gene's transcriptional activity," *id.* ¶ 124, and to "produce higher levels of EPO," *id.* ¶ 129. *See id.* ¶¶ 126-138.[111]

While this theory is intriguing—and might well have justified invocation of the reverse doctrine of equivalents—the evidence HMR/TKT presented fails sufficiently to support it.

HMR/TKT relied primarily on Dr. Kingston's testimony to elucidate its neighborhood theory. Dr. Kingston testified that the neighborhood around the EPO gene affects expression capability. *See, e.g.*, Kingston Test., R. Trial Tr. at 36. He explained that HMR/TKT uses an endogenous EPO promoter in a region that is normally set up to express EPO. Therefore,

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[111] It is clear that HMR/TKT claims its construct has a more efficient expression system—expressing more EPO per gene copy than the cells made following example 10 in Amgen's patent. *See, e.g.*, HMR/TKT's Reply Br. After Trial at 29-30. It is unclear, however, whether it is truly claiming that its process makes more EPO, as it appears from some of its submissions. Regardless, HMR/TKT never provides any support for such a contention, as will be discussed further below.

like a hotel that is positioned in the heart of the city, he argued, it is helped by its surroundings, that is, the nearby regulatory sites "all work together to help keep this gene on." *See, e.g.*, Kingston Test., R. Trial Tr. at 26-28. This is different, according to Dr. Kingston, than Amgen's process which, as explained in the specification, randomly integrates exogenous DNA, leaving the potential surroundings up to chance. *Id.* at 26-28 ("A gene that has gone into an open region that doesn't happen to be near any other regulatory elements" may have "nothing in its surroundings to help it stay on."); *id.* at 151. Dr. Kingston opined that it was the neighborhood—and not the difference in promoter strength, culture conditions, media, or cell type, or any other factors—that caused HMR/TKT's construct to express more EPO per gene copy than the cells made following example 10 in Amgen's patent. *Id.* at 29-33.

Although this testimony is compelling, it fails to persuade the Court for three reasons. First, notwithstanding Dr. Kingston's testimony to the contrary, the bulk of the credible evidence demonstrates that the endogenous regulatory sequences surrounding the EPO gene in HMR/TKT's construct are "inactive" and actually do not work with the CMV promoter to enhance EPO reproduction in the R223 cells. Dr. Wall testified that the EPO neighborhood in HRM/TKT's cells does not enhance their ability to produce EPO. Wall Test., R. Trial Tr. at 1149: 3-5, 1161-62. Specifically, he explained

> The genomic neighborhood around the EPO gene is there to constrain the expression of the EPO gene in very specific cells; and in all the rest of the cells in the body the genomic neighborhood is silent, it's shut down, it's not responsive to hypoxia. So the genomic neighborhood is not set there to somehow enhance the activity of this really robust viral promoter. Instead, it's there to exqui-

sitely restrict the level and the tissue-specific activity of the EPO gene expression.

Id. at 1161: 18-1162: 2; *id.* at 1148: 13-25, 1149: 5-9, 1162: 15-1163: 11. *See also* Lodish Test., R. Trial Tr. at 1085-86 (disagreeing with Kingston's neighborhood theory). Moreover, contrary evidence exists not merely from Amgen but also from HMR/TKT itself. In its own FDA filings, HMR/TKT admitted that the regulatory sequences surrounding the EPO gene in HMR/TKT's construct are not active and actually are bypassed. HMR/TKT's IND, Ex. 18, at 16 (stating that HMR/TKT's technology works by "bypassing regulatory DNA sequences set in the "off position"); HMR/TKT's IND, Ex. 19, at 561.

Second, Dr. Kingston—the sole exponent of the neighborhood theory—did not perform any experiment to validate his conclusions. Kingston Test., Trial Tr. at 1495: 9-1496: 16; Kingston Test., R. Trial Tr. at 189: 14-16; Lodish Test., R. Trial Tr. at 1086 (noting that there is no evidence that supports Dr. Kingston's contention); *id.* at 1096: 1-5. He merely compared HMR/TKT's R223 cell experiments with Amgen's Example 10 cell experiments. These comparisons do not, on their own, establish Dr. Kingston's conclusions. As both Dr. Lodish and Dr. Wall pointed out—and Dr. Kingston did not dispute—Dr. Kingstown compared EPO production per gene copy by looking at experiments with cells grown in different locations under different conditions by different people without controlling for other variables that could have affected the amount of EPO produced per gene copy. *Id.* at 1095-98, 1091 (explaining that Dr. Kingston's comparison did not account for the different growing conditions, different promoters, and many other variables in the experiment that are evidenced by the thousand-fold variance in data points for one construct and pointing out that Kingston relied on only a single data point); Wall Test., R. Trial Tr. at 1155, 1157-1158 (objecting to Dr. Kingston's conclusions because there is not

a reliably established significant difference; "you can't really compare these two cells. They're like apples and oranges" due to "time differences" and a "large number of variables that could affect the expression level of EPO in those cells"); *cf.* Kingston Test., R. Trial Tr. at 190-91, 199-202, 205-06 (conceding that no other experiments were conducted, that the experiments were based on a single data point, and that he could not do a statistical analysis to determine if there was an outlier, but asserting that he still considered them to be controlled experiments); Kingston Test., Trial Tr. at 1484-85, 1490-91 (acknowledging that factors other than "neighborhood" effects can affect the amount of EPO produced per gene copy). Even Dr. Kingston admitted that a failure to use controls can lead to erroneous or misleading results and that a competent technician controls for the variables that could cause certain results. Kingston Test., R. Trial Tr. at 120: 10-18, 119: 9-120: 3. Furthermore, the evidence at trial suggested that HMR/TKT's experimental data itself was inconsistent. A single data point was an 800-fold difference from all the other data points—a variance greater than the alleged 500-fold difference between the single data point for pREPO26 and the highest value reported for pREPO22. Kingston Test., R. Trial Tr. at 190: 16-25, 201: 1-10; *see also* 12-17-96 Memo from Fike to Hermentin, Ex. 165. Thus, there is no reliable experimental data supporting the contention that it is the neighborhood, as opposed to some other factor, that accounts for HMR/TKT's expression capabilities.

Third, even if HMR/TKT had proven that the genomic EPO regulatory sequences in the EPO neighborhood—and not other factors like nutritional growth conditions, limits in cellular folding, strength of promoter, number of enhancers, and the Kozak sequence—affected the amount of EPO produced per gene copy, that would not have proved a meaningful change or substantial difference in actual EPO production. *SRI Int'l*, 775 F.2d at 1123; *cf. Winans*, 56 U.S. at 342-343. The evidence shows that HMR/TKT's R223 cells do not

produce more EPO or better EPO, even though they make more EPO per gene copy than the cells made following example 10 in Amgen's patent.[112] Lodish Test., Trial Tr. at 178: 4-12; Wall Test., R. Trial at 1155: 4-9, 1156: 23- 1157: 1 (noting that the difference is not significant). Indeed, Dr. Kingston admitted that actual EPO production levels by Amgen's example 10 cells and R223 cells were comparable. Kingston Test., R. Trial Tr. at 177: 25-178: 16. Moreover, uncontradicted testimony adduced at trial shows that there was no difference in biological activity or therapeutic effects of the EPO glycoprotein ultimately secreted by the two cells. Lodish Test., Trial Tr. at 166: 15-25. Given the claims, the specification, and the absence of any language about gene copy number, how efficiently the EPO is made is simply not material.[113] HMR/TKT points to nothing in the specification or prosecution history to suggest otherwise. As both Dr. Lodish and Dr. Wall testified, a more significant comparison would be between the amounts of EPO made by the respective cells or even between the rates of expression of EPO per million cells per 24 hours in the respective parties' processes—not the amount of EPO produced per gene copy. Wall Test., R. Trial Tr. at 1155: 4-9; Lodish Test., R. Trial Tr. at 1085: 13. Moreover, even if a comparison of the amount of EPO produced per gene copy was a material one, and if such a comparison had been conducted using controls, HMR/TKT's argument would likely still fail. HMR/TKT compares its cells to the cells in an example when it is clear, as Amgen argues, that "Dr. Lin's patent describes and teaches much

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[112] Dr. Lodish pointed out that both cell types contain the same expression construct; the R223 cells simply contain more copies of it. Lodish Test., Trial Tr. at 163: 16-18. This, however, does not amount to a functional difference in the cells' ability to produce EPO. *Id.* at 178: 4-12.

[113] Even if it was material, HMR/TKT has still not met its burden because, as discussed immediately above, much evidence was presented that factors other than the neighborhood could cause the differences in EPO production efficiency and Dr. Kingston did not control for these factors.

more—including various cultured vertebrate and mammalian cells, including human cells, grown in optimized nutrient conditions having stronger and/or more numerous viral promoters and enhancers." Amgen's Reply to HMR/TKT's Findings of Fact ¶ 101; *see also* Wall Test., R. Trial Tr. at 1161: 8-13.

Had HMR/TKT proven that its new technology of using homologous recombination or endogenous activation actually worked in some substantially different way due to the neighborhood and enabled it to produce significantly more EPO or EPO that somehow differed in its biologic or therapeutic effects (which would have supported HMR/TKT's contention that its technology functions differently), it might well have demonstrated sufficient grounds for invoking the reverse doctrine of equivalents. *Cf. Scripps*, 927 F.2d at 1565 (noting that whether alleged infringer's new recombinant technology resulted in "specific activities and purity" otherwise unattainable might, if proven, provide sufficient grounds for invoking the reverse doctrine of equivalents). Here, however, HMR/TKT has not done so. It has not shown that any of these differences constitute a radical or dramatic improvement or are "so far changed in principal that they perform the function in a substantially different way." *SRI Int'l*, 775 F.2d at 1124.

Thus, despite the fact that HMR/TKT's process employs homologous recombination and endogenous DNA and produces more EPO per gene copy than Amgen's Example 10 cells, it appears that its process does exactly that which Amgen's patent teaches: it introduces a strong viral promoter and non-human enhancers to overcome the naturally restrictive neighborhood in the R223 cells. *See* Wall Test., R. Trial Tr. at 1149: 3-14, 1159: 6-1161: 13; Lodish Test., R. Trial Tr.

at 1097; Lodish Test., Trial Tr. at 165: 1-11, 178: 4-12; Kingston Test., Trial Tr. at 1382-1386.[114]

(2) Different Promoter Placement, Splice Sites, and Leader Sequences

HMR/TKT argues that it places its promoter much farther upstream of the EPO gene to be expressed than does Amgen and that this was something those skilled in the art in 1984 would not have dared to attempt. HMR/TKT's Opening Br. After Trial at 13. As a result, it contends, HMR/TKT's process for producing EPO uses primary RNA transcripts and splice sites that differ from those used in Amgen's process, and results in a different EPO mRNA in HMR/TKT's and Amgen's cells and a different primary EPO protein product. HMR/TKT's Proposed Findings of Fact at 33-36; HMR/TKT's Opening Br. After Trial at 15.

(a) Upstream Promoter Placement and Splice Sites

Although it is undisputed that HMR/TKT places its promoter much farther upstream than 44 base pairs (the position described in one example in Amgen's specification), the Court has now found that placement of the promoter further upstream of the EPO coding region and splicing out deleterious ATGs was indeed a concept known and understood to those skilled in the art at the time Amgen filed its application (1983-84).[115] Furthermore, the Court has held that Amgen's

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[114] To be clear, none of the examples requires that the EPO coding sequences be "cut away" from their native regulatory sequences. To the contrary, according to Dr. Wall, Example 10 retains a downstream native EPO regulatory sequence—the hyposix inducible element ("HIE"). Wall Test., R. Trial Tr. at 1128: 10-1129: 1.

[115] As noted earlier, HMR/TKT offers no support—except previous statements by this Court—for its assertion that no one skilled in the art could have or would have in 1984 dared to place the promoter so far upstream from the coding sequence.

process covers, adequately describes, and enables such upstream promoter placement.

In terms of the EPO splice donor sites, it is undisputed that absent the exons, the splice donor sites are the same and that the intended effect of both processes was to splice out what is in between including intervening sequences and any deleterious ATGs. *See, e.g.*, Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1-22, 1440: 19-25, 2094-2102 (admitting that what HMR/TKT labeled as its splice donor site is identical to the human splice donor site disclosed by Amgen in Figure 6). HMR/TKT argues, however, that its splice site is not the same as Amgen's because the left portion (the exon) is different. HMR/TKT's Opening Br. After Trial at 15; HMR/TKT's Proposed Findings of Fact at 35. It asserts that "it is the exon portion that matters" because it creates the leader sequence for the expressed polypeptide, that is, the exons remain to encode the polypeptide while the introns are removed. HMR/TKT's Opening Br. After Trial at 15. Amgen argues that the exon is irrelevant and not part of the splice site. Therefore, the key factual question for the Court is whether exons are included when one skilled in the art refers to the splice sites.

To the extent that the experts disagreed, the Court credits Dr. Lodish's testimony explaining that the exons are not included. Lodish Test., R. Trial Tr. at 1107-10; *id.* at 1132-33 (explaining that it is the splice donor sequence, not the splice junction, that will determine where downstream and with what corresponding DNA downstream a splice junction will splice and stating that "the splice donor is the sequence . . . that is removed during the splicing process," the splice acceptor is the sequence that is removed downstream, and "it's the regions on either side that are linked together"). This accreditation of Dr. Lodish's testimony is supported by evidence that HMR/TKT itself did not consider the hgH exon 1 to be part of the splice donor sequence. In its Investigational

New Drug Application (IND) and in its patent, HMR/TKT identifies the splice donor site to be separate from the growth hormone exon 1 sequence. *See, e.g.*, HMR/TKT's IND, Ex. 19, at 554; HRM/TKT's IND, Ex. 20, at 830; U.S. Patent No. 5,641,670 ("Treco's Patent"), Ex. 12, col. 50: 53-55; *see also* Kingston Test., Trial Tr. at 2094-2102 (conceding that this interpretation of the IND and patent is correct—that is, that HMR/TKT did not include the three nucleotides in exon 1 as part of the splice donor sequence). Moreover, in the IND, HMR/TKT identifies the splice donor sequence to be the first 10 nucleotides of intron 1: GTGAGTACTC, which is identical to the sequence in Amgen's patent. *See, e.g.*, HMR/TKT's IND, Ex. 19, at 554; HRM/TKT's IND, Ex. 20, at 830; *see also* Demonstrative Aids 7 & 8 from Lodish Rebuttal Examination, R. Trial.

Thus, as alluded to earlier in the written description analysis, this Court finds that the fair preponderance of the evidence shows, by a slight margin, that HMR 4396 uses the same splice donor site as that disclosed in Amgen's specification. Kingston Test., Trial Tr. at 1431: 10-19, 1432: 14-24, 1433: 1- 22, 1440: 19-25 (admitting that absent the exons, the splice donor sites were the same and that the intended effect was to splice out what is in between, including intervening sequences and the deleterious ATGs). The only difference is that Amgen takes the genomic EPO splice donor site disclosed in Amgen's Figure 6 and moves it upstream. Placing the promoter further upstream of DNA encoding a protein using the identical splice site is simply not a fundamental change in principal, because the intervening DNA is spliced out when the mRNA is formed. As discussed *supra*, skilled artisans could have done this at the time Amgen filed its application, and, more importantly, skilled artisans could easily have done it at the time of the alleged infringement—the relevant time period for analyzing equivalent infringement. *Warner-Jenkinson*, 520 U.S. at 37. Therefore, it is unclear how HMR/TKT can argue that its promoter place-

ment differentiates its process from Amgen's process. As the Federal Circuit pointed out when HMR/TKT made the same argument in furtherance of the reverse doctrine of equivalents with respect to the '349 product claims, the exact promoter placement or the way the accused device controls transcription is not relevant to the analysis because neither the claims nor the specification require a locational limitation. They merely call for "operative linkage," which was construed by the Court to mean "the promoter DNA is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen*, 126 F. Supp. 2d at 90. It refused to read any distance restriction in the claim term "operatively linked," because the specification does not restrict the promoter location. It merely communicates that in order to achieve "operative link[age]," what is important is placing a strong promoter upstream of the ATG initiating codon of the EPO gene and splicing out unwanted ATGs. Thus, that which HMR/TKT does was "suggested" by the patent. *Westinghouse*, 170 U.S. at 573 ("If the method pursued by the patentee for the performance of the function discovered by him would naturally have suggested the device adopted by the defendants, that is in itself evidence of intended infringement."). Thus, HMR/TKT has not shown any real difference, let alone a substantial or radical one.[116]

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[116] HMR/TKT argues that its upstream promoter placement and the difference in the type of promoter optimize its process, and it cites testimony by Dr. Lodish and Dr. Wall admitting that the location and strength of the promoter affect the promoter's activity. *See, e.g.*, HMR/TKT's Findings of Fact ¶¶ 117, 119. These arguments, however, fail to justify evocation of the doctrine for the same reasons discussed earlier. First, mere improvement or superiority is not enough. Second, it is unclear that HMR/TKT has shown any relevant optimization, since increased EPO production or quality is not claimed. Third, the location of the promoter or type of strong viral promoter are not specifically claimed or defined by the specification.

(b) Different Leader Sequences in the Primary EPO Protein Product

HMR/TKT argues that its primary EPO protein product is different from Amgen's product because it contains a hybrid leader sequence containing both hGH and human EPO amino acids, whereas Amgen's only contains EPO leader sequences. HMR/TKT's Proposed Findings of Fact at 36; HMR/TKT's Opening Br. After Trial at 15.[117] At trial, Dr. Lodish conceded that in Amgen's Example 10, exon 1 comes from the EPO gene whereas in HMR/TKT's process, it comes from the human growth hormone gene. Lodish Test., Trial Tr. at 174. He explained that the difference between the leader peptides is a "minor" one because they both function in exactly the same way and both are removed. *Id.*; *see also id.* at 433-34 (stating that the leader peptides are different but perform the same function and are ultimately cleaved); *id.* at 159-160. Evidently, exons 2-5 of the EPO structural genes are what encode amino acids in the mature secreted form of the protein. *Id.* at 173; *id.* at 160 ("[E]xon 1 . . . encodes part of the leader peptide which is removed from the cell and has no other function."). Furthermore, what is ultimately secreted from the cell is the same polypeptide with three n-linked oligosacharides, sialic acids . . . and one o-linked oligosaccharide." *Id.* at 174; *id.* at 160 ("Exon 1 . . . has no effect whatsoever on the secreted mature EPO glycoprotein."). HMR/TKT points to no evidence disputing this testimony nor does it even attempt to explain how this difference presents a change in principle from Amgen's patented process.

(3) Method of Growing Cells

HMR/TKT argues that it grows its cells in a substantially different manner from that described in the '698 patent.

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[117] This involves the step of translation. When the messenger RNA is translated, the result is a polypeptide which has a leader sequence. Kingston Test., R. Trial Tr. at 53: 2-4. During HMR/TKT's translation, the leader sequence contains both the hGH and human EPO amino acids. *Id.*

HMR/TKT's Opening Br. After Trial at 18-19; HMR/TKT's Proposed Findings of Fact at 38-41. It points out that Amgen's specification describes a process of growing vertebrate cells that uses a roller bottle system to obtain adhesion of the cell line to the bottle surface. HMR/TKT's Opening Br. After Trial at 19. HMR/TKT, on the other hand, uses an air-lift technology that "works in a completely different way from roller bottle technology". *Id.*

These arguments fail for the same reasons that all of HMR/TKT's other reverse doctrine of equivalents arguments fail. First, HMR/TKT compares its process to the method of culturing described in an embodiment in the specification instead of to the spirit and intent of the claims. Second, it has not even argued how its culturing process is changed in principle from that explicated in Amgen's patent.

The Court begins by pointing out that it has not construed the claims to require roller bottle culturing. Nor has HMR/TKT pointed to anything in the patent, specification, or prosecution history to compel it to do so. HMR/TKT simply argues that because a roller bottle system is the only type of culturing actually described in the specification, the claims should be limited to this type of culturing. The Court has already explained at length that a patent's scope is not limited to those embodiments described in the specification, absent concerns about invalidity, prosecution history estoppel, or other such grounds.

Moreover, after a careful review of the specification, it is clear that it does anything but imply that use of roller bottles is the only way to culture or grow the cells. The specification states that productivity can be improved "by appropriate cell culture techniques." '933 Patent, Ex. 1, col. 27: 7-9. Then it makes a general statement that "[the] propagation of mammalian cells in culture generally requires the presence of serum in the growth media," but that "a method" that does not contain serum can "greatly facilitate" the process. *Id.* at col.

27: 10-14 (emphasis added). The implication of these two sentences is (a) more than one culturing technique is contemplated, and (b) both serum and serum-free culturing can be used to propagate mammalian cells, but serum-free is preferred. The specification then goes on to describe one such preferred method that happens to use roller bottles. *Id.* at col. 27: 15-53. Later, the specification also teaches, in the preferred method, growing suspension cell cultures in spinner flasks--yet another type of culturing or growing process. *Id.* at col. 27: 19-21. Thus, the specification does not only teach culturing via the roller-bottle but also teaches culturing in spinner flasks.[118] Indeed, HMR/TKT's expert testimony confirms this interpretation of the specification. *See* Hancock Test., R. Trial Tr. at 259: 20-260: 21, 262: 16-263: 24 (admitting that in 1984 roller-bottles were not the only method for culturing mammalian cells and that the specification teaches growing up the suspension cell cultures in spinner flasks, which grow the cells in suspension).

Since HMR/TKT points to nothing in the patent or prosecution history to support adding a limitation to the claims, the Court refuses to do so. The equitable scope of the claim is broader than roller-bottle culturing. *Scripps*, 927 F.2d at 1581 (weighing accused device against equitable scope of the claims); Sirilla, Feddo & Antone, *supra*, at 101.

Even if the Court were to limit the claims to a roller bottle system of culturing, HRM/TKT would still fall short of making a prima facie showing that the reverse doctrine of equivalents is applicable. HMR/TKT does not even attempt to explain how using an air-lift fermenter to grow its cells (as opposed to roller bottles) justifies invoking the reverse doc-

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[118] That this other type of culturing is described during the preparatory stage does not change the analysis because, according to HMR/TKT's expert, the cells are "growing" and producing EPO in the preparatory stage. Hancock Test., R. Trial Tr. at 263: 3-264: 11. Therefore, this culturing method can be deemed part of the "growing" step described in the claims.

trine of equivalents, that is, it does not show how this difference is a "manifest departure in principle" or even novel, for that matter. *Westinghouse*, 170 U.S. 572, 579. Instead, it spent many of its precious trial minutes[119] eliciting testimony about the minute distinctions between air-lift fermenting and roller-bottle culturing. *See generally* Hancock Test., R. Trial Tr. at 232-39. For example, it showed at trial that (a) the cells circulate through the fermenter, but adhere as a layer to the surface of the roller bottles; (b) roller bottle culturing uses fetal calf serum, while the air-lift technology does not; (c) roller bottle culturing is done horizontally, while air-lift fermenting is done vertically; and (d) multiple bottles are used in roller bottle culturing, while only a single vessel is used in air-lift fermentation. *Id.* at 234, 236-40. HMR/TKT failed, however, to demonstrate that the two processes are premised on anything other than the same principle of mixing cell cultures.

Indeed, HMR/TKT did not even show that air-lift fermenting was superior let alone a substantial or radical improvement. Dr. Hancock basically testified as to how the processes were different, but said nothing about how these differences mattered. *See generally* Hancock Test., R. Trial Tr. at 232-39. True, Dr. Hancock testified there is a risk of contamination when using fetal calf serum and that the air-lift fermenter allows for more uniform monitoring and control of conditions since it only uses one vessel. *Id.* at 234-35, 241, 256; *see also id.* at 238-399. He did not, however, loop it back together. He

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[119] This trial, as indeed all civil trials in this session of the Court, was conducted pursuant to strict overall time limits established by the parties pre-trial and confirmed by order of the Court. Reasonable time limits have been confirmed by the nation's most thoughtful commentators as a trial technique that enhances the quality of justice and improves the administrative aspects of any civil trial. The Vanishing Trial, Discussion at the ABA Section on Litigation Symposium (Dec. 12-14, 2003). The Court has long followed this salutary practice. *Lareau* v. *Page*, 840 F. Supp. 920, 933-35 (D. Mass. 1993).

did not present or refer to any controlled experimental data comparing the two processes that showed that fetal calf serum caused contamination that affected the process. *Id.* at 256-57. Moreover, he did not testify as to how or even whether the additional level of control in air-lift fermenting is beneficial or superior. *Id.* at 239. He merely made some vague statements that in the air lift fermentation technology, the process could potentially be optimized because the medium can be defined. *Id.* at 242-43. Even if there had been a more concrete showing that serum-free medium was advantageous to fetal-calf serum medium, it would not have been enough to show a substantial change or manifest departure in principle. As discussed earlier, the mere fact that something is improved or better does not justify invoking the reverse doctrine. *See, e.g., Studiengesellschaft*, 726 F.2d at 728; *Phillips Petroleum Co.*, 673 F. Supp. 1278.

Further, HMR/TKT's own expert implicitly admitted that growing cells in an air-lift fermenter is *equivalent* to many culture methods including the roller bottles or spinner flasks exemplified in Amgen's patent. Hancock Test., R. Trial Tr. at 264: 12-265: 12, 261: 23-262: 24 (conceding that regardless of whether roller bottle spinner cells are used or other types of culturing techniques, the objectives are the same and can be met by mixing or agitating the cell culture by spinning, rolling, or mixing it with air bubbles from an air-lift fermenter).

As the Federal Circuit has noted many times in the past, "[e]quivalence and non-equivalence, as the terms indicate, are but opposite sides of the same coin." *SRI International*, 775 F.2d at 1125; *id.* at 1125 n.22 ("In both instances, one is dealing with whether a particular product falls within a *range* of products which the patent entitles the patentee to exclude others from making, using, or selling."); *see Westinghouse*, 170 U.S. at 568; *Texas Instruments II*, 846 F.2d at 1371; Duffy, *supra*, at 315. Since air-lift fermenting is essentially

equivalent to roller-bottle culturing and is premised on the same principle of mixing cell cultures, it cannot qualify as a "reverse equivalent." *SDS USA, Inc.*, 122 F. Supp. 2d at 541; *see also Westinghouse*, 170 U.S. at 569 (explaining that if the substance of the invention is there, "[m]ere variations of form may be disregarded").[120]

(4) HMR/TKT's Process Was Patented

HMR/TKT seems to believe that since the United States Patent and Trademark Office granted it a patent on its culturing process, the two processes must be so substantially different that the reverse doctrine of equivalents can justifiably be invoked. *See, e.g.*, HMR/TKT's Reply Br. After Trial at 28; HMR/TKT's Proposed Findings of Fact ¶ 121. While attainment of a patent may aid in making a prima facie case in support of the reverse doctrine of equivalents, *see, e.g.*, *Jewish Hosp. of St. Louis* v. *IDEXX Laboratories*, 973 F. Supp. 24, 28 (D. Me. 1997) (finding a prima facie showing met when one of three facts asserted was that the process was patented), it does not necessarily equate to such a determination. *See, e.g.*, *Nat'l Presto Indus., Inc.* v. *West Bend Co.*, 76 F.3d 1185, 1191-92 (Fed. Cir. 1996) ("The grant of a separate patent on the accused device does not automatically avoid infringement, either literal or by equivalency. Improvements or modifications may indeed be separately patentable if the requirements of patentability are met, yet the device may or may not avoid infringement of the prior patent."); *Atlas Powder Co.* v. *E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 1580-81 (Fed. Cir. 1984) (finding equivalent infringement despite the fact that the accused device was

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[120] The Court's conclusion that HMR/TKT's mode of culturing is not "so far changed in principle" or "substantially different" finds further support in the fact that HMR/TKT's expert stated that HMR/TKT itself employs roller bottle culturing in an early stage of its manufacturing process. Hancock Test., R. Trial Tr. at 265: 13-266: 13; HMR/TKT's IND, Ex. 19, at 566, 574.

separately patented). Thus, as Amgen contends, "patents are routinely granted for improvements in technology even though the practice of the technology would infringe an earlier issued patent." Amgen's Reply to HMR/TKT's Opening Br. After Trial at 29; *see also* Lemley, *Economics*, *supra*, at 1009 (not-ing that "patenting an improvement does not prevent it from infringing on the original patent" and describing three situations where "an improvement which is nonobvious in view of the prior art can still infringe on a patent which is part of that prior art"); *see also* Merges & Nelson, *supra*, at 865 ("Issuance of an improvement patent or a holding that a patent is valid but subservient to another patent is . . . common."). Indeed, here it appears that HMR/TKT's patent consists of claims that are narrower but within the scope of Amgen's broader patent since its claims relate to homologous recombinant cells comprising a targeting sequence, an "exogenous regulatory sequence, an exogenous exon, and a splice-donor site operatively linked to the second exon of an exogenous gene." Treco's Patent, Ex. 12, col. 63: 50-54. Thus, without more, the fact that its process has been patented fails to make HMR/TKT's case.

c. Conclusion

HMR/TKT has succeeded in proving that its process differs in many respects from those specifically exemplified in the Amgen's specification and even is advanced technologically in at least one way. As the Supreme Court explained in *Graver Tank*, however,

> Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents. Consideration must be given to the purpose for which [some aspect of

> the invention] is used in a patent, the qualities it has when combined with the other [aspects], and the function which it is intended to perform.

339 U.S. at 609; *see SRI International*, 775 F.2d at 1124. Here, taken together, the accumulated differences between the accused device and Amgen's invention—as described in the patent, the claims, and the specification—are not *substantial*; that is, they do not show that any principal has been *so far* changed such that it would be inequitable to view HMR/TKT's invention as within the scope of the claims of the '698 patent. *Studiengesellschaft*, 726 F.2d at 728 (considering whether there is so much dissimilarity that it would be inequitable to regard the infringing invention as within the scope of the claims); *see also Westinghouse*, 170 U.S. at 568 (considering whether the claims cease to represent the invention).

While the Court affirms the viability of the reverse doctrine of equivalents for those rare cases where the claims read on a new device or process despite its use of a new technology that makes a real difference in how the process works or what is produced, HMR/TKT has failed to meet its burden in establishing the defense here (although the neighborhood theory potentially could have carried the day, had it been thoroughly demonstrated through experimentation at trial).

5. Ultimate Conclusion Concerning Infringement of the '698 Process Patent

The Court holds that Amgen has carried its burden of proving by a fair preponderance of the evidence that HMR/TKT's process infringes the '698 patent, claims 4-9.

B. The '349 Patent: Claim 7

1. Background

In *Amgen I*, the Court held that HMR/TKT did not literally or equivalently infringe claim 7, the process claim, of the

'349 patent. *Amgen I*, 126 F. Supp. 2d at 122.[121] In reaching this determination, the Court compared the accused process to the preferred embodiment in the specification and concluded that "[HMR/]TKT's process for producing erythropoietin differs markedly from that disclosed by Amgen's specification" because it "utilizes the endogenous rather than exogenous EPO gene" and it "places its promoter upstream from, rather than adjacent to, the EPO gene." *Id.* The Federal Circuit, as it did with the Court's holding of infringement of the '698 patent, vacated this holding and remanded it so that the Court could analyze infringement by comparing the accused process to the properly construed claims themselves. *Amgen II*, 314 F.3d at 1313, 1347, 1351.

Since the Court heard the entirety of both parties' arguments and evidence concerning the '349 patent at the first trial, no new evidence with respect to this patent was taken on remand. The parties, however, were given the opportunity to brief the issues remanded to this Court in pre and post-trial memoranda. Before the Court are both parties' motions for judgment pursuant to rule 52(c) [Doc. Nos. 674 & 686].

In HMR/TKT's motion for judgment pursuant to rule 52(c), it argued a new defense, the reverse doctrine of equivalents. Although the Court allowed the defense as it related to the '698 patent, it did not definitively do so for the '349 patent, because the procedural postures of the two patents were different. HMR/TKT never had a chance to present its case of non-infringement with regard to the '698 patent in *Amgen I*, but it did with regard to the '349 patent. As it ends up, this procedural dispute is moot. Even if the Court were to allow the defense at this stage, it would fail for lack of merit.

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[121] As discussed earlier, the Court held and the Federal Circuit affirmed that HMR/TKT literally infringed claims 1, 3, 4, and 6. *Amgen I*, 126 F. Supp. 2d at 117-18; *Amgen II*, 314 F.3d at 1351-52. Thus, the only issues remaining regarding this patent concern claim 7, the process claim.

2. The Claim At Issue

Amgen's '349 patent contains six product claims regarding types of vertebrate cells grown in culture and one process claim, claim 7. The issue is whether HMR/TKT infringed claim 7, the process claim:

> A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6.

'349 Patent, Ex. 1, col. 38: 34-36.

3. Literal Infringement

a. Discussion

Since literal infringement of claims 1, 2, 4, and 6 has been established and affirmed, *Amgen II*, 314 F.3d at 1352, 1358, to prevail on this issue, Amgen need only show by a fair preponderance of the evidence that HMR/TKT's process for producing EPO comprises "culturing under suitable nutrient conditions, vertebrate cells." Here, it is clear that Amgen has met its burden.

First, Dr. Lodish specifically testified that "I guess there is no dispute that [HMR/TKT's] cells are cultured and they're clearly vertebrate cells." Amgen's '349 App., Tab I (Lodish Test., Trial Tr.) at 300: 22-301: 8. HMR/TKT's assertion that Dr. Lodish's testimony makes clear that he was only guessing does not cast any affirmative doubt on Dr. Lodish's statements, which this Court credits.

Second, as discussed earlier, the Joint Pretrial Memorandum itself states that HMR/TKT's HMR 4396 is produced by "growing, under suitable nutrient conditions R223 cells," Amgen's '349 App., Tab M (4/26/00 Corrected Joint Pretrial Mem.), ¶ 25, and that its cells are cultured, *id.* ¶ 13 ("HMR 4396 is produced from the R223 cell line grown in culture."). Since HMR/TKT has admitted in various contexts that culturing and growing basically mean the same thing, it has

implicitly admitted that its process literally infringes claim 7.[122]

Last, this Court's factual findings support the holding that HMR/TKT's process cultures the cells. In finding literal infringement of claims 1 and 4 of the '349 patent, this Court found that HMR/TKT's R223 cells are "capable, upon growth in culture, of producing erythropoietin in the medium of their growth in excess of 100 units of erythropoietin per 10 cells in forty-eight hours as determined by RIA (radioimmunoassay)," just like Amgen's cells. *Amgen I*, 126 F. Supp. 2d at 119. Thus, the Court finds that HMR/TKT's cells are cultured.

Tellingly, HMR/TKT did not even argue in its post-trial submissions that its process did not literally infringe claim 7 of the '349 patent.

b. Conclusion Concerning Infringement: '349 Patent, Claim 7

Amgen has shown by a fair preponderance of the evidence that HMR/TKT's HMR 4396 literally infringes claim 7 of the '349 patent.

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[122] In one of its claim construction submissions, HMR/TKT proffered that "culturing under suitable nutrient conditions" means the same things as "growing in vitro, under suitable nutrient conditions. 10/18/99 Amgen's Claim Construction Submission, Ex. A, at 5. In its memorandum in support of its step-plus-function arguments regarding the '349 and '698 patent, HMR/TKT asserted the exact same arguments with regard to the step of growing and the step of culturing.

Experts also used the two words interchangeably. Dr. Tlsty stated that he had been "growing and culturing cells since [he] was an undergraduate." Amgen's Opp'n at 13; Tlsty Test., Trial Tr. at 832: 1-16; *see also* HMR/TKT's IND, Ex. 19, at 574 (describing the culturing of HMR/TKT's R223 cells).

4. Reverse Doctrine of Equivalents

HMR/TKT presented the exact same arguments in furtherance of its reverse doctrine of equivalents arguments for the '349 patent as it did for the '698 patent. Given that it points to nothing in the claims or prosecution history of the '349 patent specifically in support, and the specifications are the same as between the two patents, the above analysis with respect to the '698 patent applies here.[123]

5. Ultimate Conclusion Concerning Infringement of Claim 7 of the '349 Patent

The Court rules that Amgen has shown by a fair preponderance of the evidence that HMR/TKT's process literally infringes Amgen's '349 patent. Therefore, HMR/TKT's Fed. R. Civ. P. 52(c) motion regarding infringement of the'349 patent [Doc. No. 686] is DENIED and Amgen's Fed. R. Civ. P. 52(c) motion regarding infringement of the '349 patent [Doc. No. 674] is ALLOWED.

VI. VALIDITY CHALLENGES UNDER 35 U.S.C. §§ 102(a) & 103

HMR/TKT argues that the asserted claims of the '422, '080, '698, and '349 patents are either anticipated or rendered obvious by Sugimoto, Goldwasser, or both. Since these patents are presumed valid, HMR/TKT bears the burden of proving its contentions by clear and convincing evidence. 35 U.S.C. § 282 (2000); *Amgen II*, 314 F.3d at 1335.

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[123] Indeed, it is even less appropriate to apply the reverse doctrine of equivalents with respect to the '349 patent than with respect to the '698 patent, since these same reverse doctrine arguments were made and rejected by the Federal Circuit with respect to the product claims of the '349 patent, and, as mentioned earlier, HMR/TKT has not adduced, nor has the Court found, any case law suggesting that process patents should be analyzed differently than product patents.

A. Sugimoto

1. Background

a. Overview of Sugimoto

U.S. Patent No. 4,377,513 (Sugimoto's patent) was filed in 1981 and issued to Sugimoto on March 22, 1983. Sugimoto's patent, Ex. 2229, at 1. Sugimoto claims a process for producing human erythropoietin comprising "multiplying human lymphoblastoid cells capable of producing erythropoietin by transplanting said cells into a non-human warm-blooded animal body," or, alternatively, multiplying said cells "by allowing said cells to multiply with a device by which the nutrient body fluid of a nonhuman warm-blooded animal is supplied to said cells," and allowing the cells multiplied by either of the above multiplications procedures to release human erythropoietin. *Id.* at col. 6: 46-59. Put another way, Sugimoto claims that when a human cell line that produces EPO is fused with a human lymphoblastoid cell line, the resulting fused cells produce higher amounts of EPO in culture than the original fusion partners. *Amgen I*, 126 F. Supp. 2d at 108. Sugimoto also advises that (1) conventional techniques can be utilized to achieve purification; and (2) human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Sugimoto's patent, Ex. 2229, col. 3: 50-55; col. 3: 66-4: 2.

b. The Court's Decisions in *Amgen I*

(1) Anticipation

This Court held that HMR/TKT failed to show by clear and convincing evidence that Sugimoto's patent anticipated Amgen's '422, '080, and '349 patents. *Id.* at 110. In support of this holding, it found that Sugimoto was not enabled and that none of the cited references disclose each and every limitation of any of Amgen's individual claims. *Id.* at 109. With respect specifically to claim 1 of the '422 patent, the

Court found that none of the cited references disclose a therapeutically effective amount of EPO or the purification of human EPO from mammalian cells grown in culture. *Id.*

(2) Obviousness

Because the Court had already held that HMR/TKT failed to prove that Sugimoto was enabled, it held that Amgen's claims were also not invalid due to obviousness. The Court noted in a footnote, however, that had the Court found the Sugimoto patent enabled, it would have "go[ne] a long way toward proving HMR/TKT's obviousness defense." *Id.* at 114. This is because the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. The Court noted that if one of ordinary skill could actually make the EPO-producing cells described in the Sugimoto patent, a point on which HMR/TKT failed to persuade this Court, such a combination of prior art material might render invalid the pharmaceutical composition claims of the '080, and '422 patents. *Amgen I*, 126 F. Supp. 2d at 114 n.29. Finally, the Court noted that secondary considerations also applied to support the Court's findings of non-obviousness.

c. The Federal Circuit's Opinion

The Federal Circuit ruled that the Court erred in placing the burden of proving enablement of Sugimoto on HMR/TKT. *Amgen II*, 314 F.3d at 1354. The Federal Circuit explained that in prosecution of a patent, the examiner can reject applications as anticipated by prior art without first having determined whether that application had been enabled. The patent applicant can then overcome such a rejection by proving that the prior art had itself not been enabled. The Federal Circuit reasoned that this type of burden shifting was appropriate in this context as well. Therefore, it held "that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and

claimed) material in the prior art patent defendant asserts against a plaintiff." *Id.* at 1355.[124] The patentee, however, may prove nonenablement by a fair preponderance of the evidence. *See id.* Thus, the Federal Circuit concluded, Amgen is the party that bears the burden of proving the non-enablement of Sugimoto. *Id.*

The Federal Circuit noted that the Court could not have found that Amgen met its burden based solely on Dr. Erslev's testimony that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by Sugimoto procedure." *Id.* at 1356. "The mere fact that no one has so used the Sugimoto process is only minimally probative of non-enablement: a conclusion that no one *could have* used Sugimoto." *Id.* at 1356. Moreover, the Federal Circuit stated, the fact that Amgen argued non-enablement of Sugimoto before the patent examiner during prosecution of Amgen's patents is only minimally probative of the issue since this was only one argument out of many and "we cannot assume the acceptance of every argument presented during prosecution." *Id.* Thus, the Federal Circuit concluded that Amgen had not presented evidence sufficient to meet its burden.

The Federal Circuit clarified that the Court's error was harmless for the most part because the Court had conducted a detailed anticipation analysis. With respect to claim 1 of the '422 patent, however, the Federal Circuit directed the Court to consider, on remand, whether it is novel over Sugimoto in light of the Court's new definition of "therapeutically effective" while being "mindful of the principle that source limitations cannot impart novelty to old compositions." *Id.*

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[124] As is so frequently the case in the patent area, this is not a true presumption at all, *see* Fed. R. Evid. 301, but rather a burden shifting mechanism that places the burden of proving nonenablement on the patentee. For criticism of this recurrent imprecision in language, *see Amgen III*, 287 F. Supp. 2d at 131.

Additionally, the Federal Circuit remanded to this Court the issue of obviousness in light of Sugimoto, because a reference need not be enabled to prove invalidity under section 103. *Id.* at 1537.

2. The Claims at Issue

HMR/TKT argues that Sugimoto (1) anticipates claim 1 of the '422 patent and claims 6 and 9 of the '698 patent and (2) renders obvious claim 1 of the '422 patent, claims 2-4 of the '080 patent, and the asserted claims of the '349 and '698 patents.

3. Discussion

a. Anticipation: Does Sugimoto Anticipate Any of the Asserted Claims of the '422 and '698 Patents?

"[I]nvalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc.* v. *Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (citing *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999)); *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The invention at issue must be identical to that in a single prior art reference and it must be shown in as complete detail. *Richardson* v. *Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Determining whether a patent is invalid by anticipation in prior art is matter of fact, *Advanced Display*, 212 F.3d at 1283, and the burden is placed on the party trying to prove anticipation. *Robotic Vision Sys., Inc.* v. *View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999). Hence, here HMR/TKT must prove anticipation by clear and convincing evidence.

(1) Has Amgen Shown that Sugimoto Was Not Enabled?

As the Federal Circuit explained in *Amgen II*, "a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to enable one of skill in the art to reduce the disclosed invention to practice." 314 F.3d at 1354 (internal quotations and citations omitted). Therefore, if Amgen shows by a preponderance of the evidence, that it "present[ed] evidence of nonenablement that [this Court] finds persuasive, the [Court] must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption [of enablement] has been overcome." *Id.* at 1355.[125]

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[125] HMR/TKT argues that Amgen's burden of proof is higher than proof by a fair preponderance of the evidence. *See* HMR/TKT's Reply Br. After Trial at 4 n.* (claiming it is one of "persuasive evidence"). The Court disagrees. First, it is unclear to what standard HMR/TKT believes Amgen should be held, since proof by a fair preponderance is by its very nature "persuasive." Second, the Federal Circuit indicated in *Amgen II* that the burden should be commensurate with that required of an applicant, before the PTO, to overcome a rejection for anticipation by proving non-enablement of the prior art. The Federal Circuit held that:

> an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. . . . Like the applicant in *ex parte* prosecution, . . . the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art.

Amgen II, 314 F.3d at 1355. Before making this holding, the Federal Circuit quoted the following from *In re Sasse*, 629 F.2d 675, 681 (C.C.P.A. 1980): "[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a *preponderance of the evidence.*" *Amgen II*, 314 F.3d at 1355 (quoting *In re Sasse*, 629 F.2d at 681) (internal quotation marks omitted) (emphasis added).

As applied to this case, the conclusion that Sugimoto is enabled may be rebutted by Amgen if it shows by a fair preponderance of the evidence

For the following reasons, the Court finds that Amgen has shown by a preponderance of the evidence that Sugimoto is not enabled—that is, that Sugimoto's specification does not teach skilled artisans how to make and use the entire scope of the claimed invention without undue experimentation. *See* 35 U.S.C. § 112, ¶ 1 (2000); *Genentech*, 108 F.3d at 1365 (quoting *In re Wright*, 999 F.2d at 1461); *Plant Genetic Systems*, 315 F.3d at 1339 (same).

(a) The Starting Materials Were Neither Described Nor Made Available to the Public

First, the Sugimoto starting materials were not deposited, not described so that one skilled in the art could obtain them, and not otherwise made available to the public. Both Dr. Lodish and Dr. Green testified that Sugimoto's failure to deposit the starting materials, or to make them available to the public in some way, was critical in this case, because Sugimoto also failed to describe the starting kidney cells in a manner that would enable one skilled in the art to reproduce the method. *See* Lodish Test., R. Trial Tr. at 287: 3-288: 16 (explaining that Sugimoto only loosely describes the kidney tumor cells as "carcinomas," when he should have characterized the cells as to karyotype and morphology so that one could repeat the experiments); Green Test., R. Trial Tr. at 421: 4-422: 2 (hypothesizing that one reason why HMR/TKT's attempts to reproduce Sugimoto's hybridization failed

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that it is not. *But see Halliburton* v. *Weatherford*, No. 302CV1347-N, 2003 WL 22017187, at *1-*2 (N. D. Tex. Aug. 26, 2003) (interpreting *Amgen II* to teach that the patentee only has the burden of going forward to pre-sent some material evidence which places the enablement of the prior art in question, i.e., the burden of production); *Abbott Labs.* v. *Diamedix Corp.*, 969 F. Supp. 1064 (N.D. Ill. 1997) (same); Chisum, *supra*, § 3.04(1)(b)(v) at 3-102, 3-103. While these sources are faithful to the import of the word "presumption" in the Federal Rules of Evidence, this Court reads *Amgen II* to shift the burden of persuasion as well.

might be that HMR/TKT was unable to obtain the starting kidney tumor line described by Sugimoto).

That this failure to teach how to obtain the starting materials or to deposit them was debilitating is evidenced by both parties' unsuccessful attempts to procure such cells. Amgen, after many attempts, was unsuccessful at locating or obtaining any of the human kidney tumor cells used by Sugimoto or any cells capable of producing EPO at the levels reported by Sugimoto in his patent. Lin Test., R. Trial Tr. at 562: 19-563: 11.[126] Moreover, as this Court found in *Amgen I*, after an arduous search, even HMR/TKT's star witness, Dr. Heartlein, was unable to obtain any of the human kidney tumor cells used by Sugimoto, 126 F. Supp. 2d at 109; Heartlein Test., Trial Tr. at 1812: 10-1813: 13; 1826: 5-1827: 24, and was unable to find any prior art EPO-producing cell lines that could be fused successfully to lymphoblastoid cells, Green Test., R. Trial Tr. at 427: 10-25.

HMR/TKT urges that Dr. Heartlein did not duplicate Sugimoto and, therefore, that his experiments cannot be used to show that Sugimoto was not enabled. *Johns Hopkins Univ.* v. *CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998) ("A party who wishes to prove that the claims of a patent are not enabled by means of a failed attempt to make the disclosed invention must show that the patent's disclosure was followed."). As pointed out in *Amgen I*, however, the reason Dr. Heartlein did not duplicate Sugimoto was that he could not do so—he could not obtain starting materials that produced EPO at the levels disclosed in the examples of Sugimoto's patent.

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[126] Evidently, Amgen even tried to purchase the starting materials and the hybrid cells directly from Sugimoto's assignee, Hayashibara Company, Ltd. *See* Rathmann Test., R. Trial Tr. at 599: 8-13. While it may be, as HMR/TKT asserts, that Amgen simply did not offer a large enough incentive to retrieve the starting materials, the fact remains that no one skilled in the art was able to obtain them in any manner, i.e., via deposit, financial incentive, or experimentation.

Amgen I, 126 F. Supp. 2d at 109. Therefore, Dr. Heartlein's failed experiments are relevant to the analysis.

HMR/TKT argues that EPO-producing cells such as the human cell line that Goldwasser obtained from Abbott and from the American Type Culture Collection (ATCC) were available to the public and that, as of 1984, several groups of researchers had reported human kidney tumor cells capable of production of human EPO. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 281-85; HMR/TKT's Response to Amgen's Proposed Conclusions of Law and Findings of Fact ¶ 21. The evidence shows, however, that these cells were not comparable to the starting materials reported by Sugimoto. Lin Test., R. Trial Tr. at 562: 19-563: 11 (testifying that Amgen was never successful in obtaining EPO producing human cells or tissue sources). The Abbott cells were normal embryonic kidney cells, not kidney tumor cells, and they did not produce EPO. *Id.* at 541-42; Amgen Project Update, Ex. 234 (providing that Abbott cells did not make EPO). None of the cells Amgen obtained from the ATCC made EPO or could be induced to produce EPO at the levels reported in Sugimoto. Lin Test., R. Trial Tr. at 559: 21-560: 2; 1/20/83 Memo from Browne to Distribution, Ex. 235; Excerpts from Lab Notes, Ex. 236; 3/23/83 Summary Notes from Lin, Ex. 237. As to the other reported EPO producing kidney tumor cells, Dr. Sherwood would not make her cells available, Lin Test., R. Trial Tr. at 540, and Dr. Green testified that none of the cell lines made appreciable amounts of EPO, Green Test., R. Trial Tr. at 421, 471: 6-19, 478: 3-15 (explaining that he was not aware that any of these researchers showed that production of EPO was sustained to the same level over time, and testifying that in 1984, several groups of researchers had reported human kidney tumor cells capable of production of human EPO, but they were "all poor producers of the EPO"); Joseph W. Eschbach, *The History of Renal Anemia (Anemia and Erythropoietin)*, Nephrology 4:279-287 (1998), Ex. 48, at 280 (noting that Lin's invention was a "difficult feat"

because, *inter alia*, "there was no source of erythropoietin mRNA").

While it is true, as HMR/TKT points out, that Sugimoto's method is not limited to starting cells that produce a certain threshold amount of EPO, even HMR/TKT itself was unable to find *any* prior art EPO-producing cell lines that could be fused successfully to lymphoblastoid cells to do as Sugimoto claimed. *Amgen I*, 126 F. Supp. 2d at 109; Green Test., R. Trial Tr. at 421: 18-422: 2; 427: 10-25. Further, HMR/TKT points out that Sugimoto claimed that *any* human cells (and specifically any human kidney tumor cells) capable of producing human erythropoietin could be used in his method. *See, e.g.*, Sugimoto Patent, Ex. 2229, at col. 6: 60-68. Yet no one was successful in finding any starter cells that worked—regardless of their EPO production capabilities. This is significant because enablement must be coextensive with the scope of the claims. *Genentech*, 108 F.3d at 1365; *Plant Genetic Systems*, 315 F.3d at 1339.

Although it is not always necessary to deposit starting materials, *Wands*, 858 F.2d at 736; 35 U.S.C. § 112, deposit is required "[w]here an invention depends on the use of living materials such as microorganisms or cultured cells" and it is "impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure." *Wands*, 858 F.2d at 735; *see* Deposit of Biological Materials for Patent Purposes, 52 Fed. Reg. 34,080, 34,084 (Sept. 9, 1987) (noting that a deposit may be required to satisfy enablement requirements of section 112); *see also Chugai*, 927 F.2d at 1211 (discussing circumstances where a deposit may be required). Here, as Dr. Lodish explained, without access to or adequate disclosure of the starting materials, "one could not begin to repeat [Sugimoto's] experiments." Lodish Test., R. Trial Tr. at 289: 16-290: 18l. Therefore, undue experimentation would necessarily be required. *Genentech*, 108 F.3d at 1366 ("[W]hen there is no

disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required.").

(b) Sugimoto Did Not Teach How To Select EPO-Producing Hybrid Cells

Second, Sugimoto neither deposited his putative "hybrids" nor taught how to select true hybrids. Dr. Green's testimony that the formation of hybrid cells—incorporating the material of two parental nuclei into a single nucleus—is "a rare event," went undisputed. *See* Green Test., R. Trial Tr. at 414: 1-8, 415: 2-9. Because most of the cells in a culture following a fusion event are not true hybrids, use of a selection method to remove all cells which are not hybrids is a very important step. *Id.* at 414-16. Sugimoto did not describe any selection method. As a result, according to Dr. Green, if skilled artisans tried to reproduce his experiments as described, "they would have no benefit of the selective system and therefore the amount of work which would be required might make it impossible for them to succeed in isolating such a hybrid." *Id.* at 422: 21-25; *see also Elan Pharms., Inc.* v. *Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) ("The determination of what level of experimentation is 'undue,' so as to render a disclosure non-enabling, is made from the viewpoint of persons experienced in the field of the invention.").

Although Dr. Green admitted that methods to select hybrid cells were available to those skilled in the art at the time, Green Test., R. Trial Tr. at 423: 14-16, 507, he explained that execution of the methods was not routine, because the methods sometimes worked and sometimes did not, and that without publishing which methods to use and whether they worked, "there's no reason to suppose that you can apply it routinely to any combination of cells and have it work correctly." *Id.* at 425: 3-5; *see id.* at 420: 10-14, 422: 16-25, 424: 19-425: 5, 520: 2-24. According to Dr. Green, this lack

of selection method, along with the fact that Sugimoto neither deposited nor characterized the cells, i.e., proved that they were hybrids, posed great difficulties to one skilled in the art attempting to reproduce the procedure. *Id.* at 425: 22-426: 8.[127]

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[127] Amgen also tried to argue that Sugimoto's failure to confirm hybrid formation or identify what confirmation method was used suggests that Sugimoto is not enabled. Dr. Green, however, agreed with Dr. Kingston that procedures for characterizing the selected cells were well known to those of skill in the art as of 1980-1984. *See, e.g.*, Green Test., R. Trial Tr. at 392: 23-393: 4, 413: 23-416: 22, 507: 11-13; Kingston Test., R. Trial Tr. at 92: 24-93: 16. While the failure to confirm hybridization leads to skepticism about Sugimoto's claims, there was, by contrast with selection methods, no suggestion that carrying out these well-known confirmation techniques was difficult or posed additional problems.

For similar reasons, Amgen's argument that Sugimoto is not enabled because he did not teach how to grow his cells in *in vitro* cell culture fails. *See, e.g.*, Amgen's Post-Trial Br. at 11, 12. Although Dr. Lodish testified on remand that some types of kidney cells are not capable of growth in culture with only routine experimentation, Lodish Test., R. Trial Tr. at 337: 24- 341: 10, he had testified during the first trial that one of ordinary skill in the art as of 1984 could adapt a vertebrate cell line to continuous growth in culture with only routine experimentation, Lodish Test., Trial Tr. at 535-36. Moreover, Amgen points to no evidence or experiments, other than Dr. Lodish's unsubstantiated and contradictory testimony, that undue experimentation would be required to adapt the cells in Sugimoto's patent to grow in culture. *See Bruning* v. *Hirose*, 161 F.3d 681, 686 (Fed. Cir. 1998) ("Conclusory and speculative testimony by . . . expert witnesses will not suffice [to show enablement]."); *cf. Telemac Cellular Corp.* v. *Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) ("Broad conclusory statements offered by . . . experts are not evidence.").

That Dr. Green did not believe that Sugimoto actually achieved growth in culture as reported does not prove that Sugimoto did not enable the process. As discussed earlier in the context of the enablement of Amgen's patents, it is not necessary that a disclosed invention have actually been made or even actually attempted. *See Donahue*, 766 F.2d at 534; *Chugai*, 927 F.2d at 1213. Instead, "what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the inven

HMR/TKT attempts to rely on Dr. Kingston's testimony to lessen the weight the Court accords Dr. Green's testimony. This attempt is unsuccessful because HMR/TKT points to no testimony by Dr. Kingston addressing selection methods specifically, let alone the potential problems identified by Dr. Green. Furthermore, although the Court has indeed considered both Dr. Kingston's and Dr. Green's testimony regarding the amount of experimentation due, *Elan Pharmaceuticals*, 346 F.3d at 1055 (citing *Enzo*, 188 F.3d at 1373-74), it gives more weight to Dr. Green's testimony, because he is undisputedly the more experienced professional in this specific area. *See, e.g.*, Kingston Test., R. Trial Tr. at 128: 2-8 (agreeing that Dr. Green is a "world-renowned expert on somatic cell fusion" and more expert than Dr. Kingston himself in that area).[128]

Moreover, that these deficiencies were debilitating to those skilled in the art trying to reproduce the procedure, and thus required undue experimentation to be overcome, is supported by HMR/TKT's failed attempt to repeat Sugimoto's process to obtain an EPO-producing hybrid cell. Green Test., R. Trial Tr. at 427: 10-22. Dr. Heartlein could not even obtain a putative hybrid when he used multiple selective markers, which make the job of selection easier. *Id.* at 427: 10-428: 12 (not-

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tion." *Id.* (internal citations omitted). Thus, as to this argument, the evidence fails to prove Amgen's point.

[128] Dr. Kingston defined a person of ordinary skill in the field of molecular and cell biology as someone who had a relevant PhD and roughly two years of experience working in the area. Kingston Test., R. Trial Tr. at 128: 12-14. Sugimoto filed his patent application in 1980. *Id.* at 17-24. Dr. Kingston himself was in the second year of his postdoctoral work in 1983, having received his PhD in 1981. At the time Sugimoto's patent application was filed—the relevant time period for determining whether Sugimoto was enabled—Dr. Kingston was not even considered one skilled in the art. *Plant Genetic Systems*, 315 F.3d at 1340 (stating that enablement is determined as of the effective filing date of the patent); *Hogan*, 559 F.2d at 604 (same).

ing that he tried unsuccessfully with one marker ten times and then with multiple markers twenty-seven separate times, finding no putative hybrids on any occasion). While it is true, as mentioned earlier, that Dr. Heartlein did not exactly duplicate Sugimoto's process, he *could not* for the reasons stated above. Morever, as Dr. Green pointed out, even when he used advanced technology, had even more resources at his disposal than Sugimoto had, and had every incentive to achieve, he could not make any hybrid cells. *Id.* at 430: 3-7. Thus, the evidence shows that undue experimentation would have been required to select a hybrid human kidney tumor/lymphoblastoid cell having the EPO-producing properties reported by Sugimoto. *See Genentech*, 108 F.3d at 1366 ("[W]hen there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.").

(c) Purification of EPO To Be Used To Treat Anemia Was Claimed But Not Taught, and Prior Art Techniques Were Insufficient

Third, Sugimoto did not enable a purification method. Sugimoto's specification states that "conventional procedures" for purification may be used to purify EPO from the lysate produced in Sugimoto's experiments and can be used "in the prevention and treatment of human diseases such as anaemia." Sugimoto's patent, Ex. 2229, at col. 3: 50-65, col. 3: 66-4: 2. HMR/TKT's experts rendered opinions that an ordinarily skilled artisan, combining procedures of Yanagawa, Chiba, and Erslev, could have purified EPO from serum or cell culture medium. *See, e.g.*, Erslev Test., Trial Tr. at 1751: 15-1754: 3; Robbins Test., Trial Tr. 1984: 7-1987: 5; Matsudaira Test., R. Trial Tr. at 910-14. Notwithstanding this

testimony, the Court is persuaded that one of ordinary skill in the art could not have used the prior art purification methods to purify to substantial homogeneity the EPO produced in tumor cell cultures.

Given the state of the art and the skill level at the time, purification of EPO in the context of the Sugimoto patent was not as simple as it seemed; that is, it was not simply a matter of applying *generic* protein purification procedures already well known in the art to purify EPO produced in tumor cell cultures. *See Wands*, 858 F.2d at 737 (noting that the state of the art and level of skill are factors to be considered in the enablement decision). This Court was not convinced during *Amgen I*—nor is it convinced now—that one of ordinary skill could have used the Yanagawa or Chiba purification methods to purify to substantial homogeneity the EPO produced in the tumor cell cultures. *Amgen I*, 126 F. Supp. 2d at 115 (noting as much in support of the conclusion that HMR/TKT failed to show by clear and convincing evidence that the pharmaceutical compositions claimed in the '933, '080, and '422 patents were rendered obvious by prior art). Dr. Green testified that Sugimoto's claim that other methods can be used to obtain human EPO preparation of high purity was "embarrassing[]" because it was "quite impossible." Green Test., R. Trial Tr. at 505: 6-16. He explained that as a scientist, he had to "examine the basis for Sugimoto's statements," and he found them "very deficient." *Id.* at 506: 5-7; *see Wands*, 858 F.2d at 738 (citing the amount of direction in the patent as one of the factors to consider in determining whether undue experimentation is required). Dr. Bradshaw gave specific examples why Yanagawa's purification method could not be used. He explained that the antibody in Yanagawa was not available and could not be substituted and that Yanagawa used an intermediate that would have denatured the EPO protein, potentially resulting in an incorrectly folded molecule. Bradshaw Test., Trial Tr. at 2717: 22-2718: 18, 2721: 4-21. There is also evidence that HMR/TKT's Dr. Erslev did not

believe that prior art purification methods could easily be combined to purify EPO. Three years after Sugimoto's disclosure, he stated in the book *Hematology* that "[r]eplacement therapy with erythropoietin, the most rational approach to the treatment of the anemia of chronic renal failure, unfortunately still lies in the future." Allan J. Erslev, *Anemia of Chronic Renal Failure*, in Hematology (3rd ed. 1983), Ex. 249, at 422.

Moreover, no one to this day has been reported as being able successfully to purify to homogeneity therapeutically effective human EPO from non-recombinant cells grown in culture, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure. Even HMR/TKT's witnesses, Dr. Matsudaira and Dr. Erslev, admitted this. Matsudaira Test., R. Trial Tr. at 930: 16-23; Erslev Test., Trial Tr. at 1755: 17-1756: 3.[129] As this Court pointed out in *Amgen I*, "in light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling then he would have won that lucrative race." 126 F. Supp. 2d at 108; *see also Genentech*, 108 F.3d at 1367 (concluding undue experimentation was needed based, in part, on the fact that the method was not used to make the claimed product for nearly a year). That Sugimoto's assignee had actually discontinued the project further supports the conclusion that Sugimoto's experiments were not enabling. 9/27/82 Rathmann Memo Memorializing Meeting with Assignee, Ex. 239, at 1 (characterizing the program as inacti-

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[129] Although the Federal Circuit made clear that this fact alone is not sufficient to prove non-enablement, *Amgen II*, 314 F.3d at 1355, it acknowledged that it did have some probative value. Moreover, when analyzing this aspect of the case, the Federal Circuit was under the misunderstanding that Dr. Erslev was Amgen's witness when in actuality he was HMR/TKT's witness. Furthermore, the Court does not rest its decision on this fact alone but also on the many other reasons discussed above.

vated and "dormant").[130] Moreover, the experiments of HMR/TKT's star witness, Dr. Heartlein, affirm that undue experimentation would be required to produce results similar to those reported by Sugimoto. As discussed in *Amgen I*, after many attempts, Dr. Heartlein could not identify any clones producing EPO in fusions involving the HEpG2 cells. As HMR/TKT points out, the Sugimoto patent is not limited to certain types of EPO-producing cells, and, therefore, this failure alone indicates that Sugimoto's patent is not enabled. *Genentech*, 108 F.3d at 1366.[131]

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[130] While this memorandum contains inadmissible hearsay, Fed. R. Evid. 801, it was admitted without objection, *see* R. Trial Tr. at 604-06, and is thus entitled to full probative weight. The confirming testimony to which objection was properly raised, Rathmann Test., R. Trial Tr. at 599: 8-13 (testifying that the assignee had said that the project had been discontinued); *id.* at 602: 8-14 (explaining that the assignee had abandoned the program so he attempted to offer money to try to retrieve some cells), was admitted only for the fact of communication (relevant on the issue of Amgen's ability to obtain the cells) and plays no part in this aspect of the analysis.

[131] In addition, Amgen argues strenuously that there is no evidence that Sugimoto actually accomplished what he claimed, that is, there is no evidence that he purified the EPO or for that matter that the lysate produced from the cells actually contained human EPO—let alone EPO that would have been therapeutically effective. *See, e.g.*, Amgen's Proposed Findings of Fact and Conclusions of Law ¶ 37; Amgen's Post Trial Br. at 12-13; Amgen's Reply to HMR/TKT's Opening Br. at 8; Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶ 220. In support, Amgen points out that Sugimoto never claims in the specification actually to have purified the EPO, to have made an EPO pharmaceutical composition, or to have administered it to any patient in need of EPO treatment. Sugimoto Patent, Ex. 2229, col. 3: 51-65; Green Test., R. Trial Tr. at 492: 5-12. Indeed, even HMR/TKT's Dr. Heartlein conceded that Sugimoto did not purify what he called EPO and that there was no evidence that Sugimoto's protein was ever formulated into a pharmaceutical composition or that the protein actually would be suitable as a pharmaceutical. Heartlein Test., Trial Tr. at 1820: 22-25; 1821: 7-11; 1824: 20-1825: 3.

The Court agrees that, given the lack of sufficient controls (attested to by various experts) and the reliance only on the Cotes Assay, Sugimoto's

Thus, given the state of the art and the level of skill at the time—proven by testimony about the prior art and subsequent art—Sugimoto's failure to provide any guidance as to what combination of purification techniques is likely to produce substantially homogenous human EPO from Sugimoto's cell extracts that could potentially be used to treat patients means his patent is nothing more than an "invitation" to experiment—and this is simply not sufficient to satisfy the enablement requirement. *Enzo*, 188 F.3d at 1374; *see also Elan Pharmaceuticals*, 346 F.3d at 1055 ("The disclosure in an assertedly anticipating reference must be adequate to enable possession of the desired subject matter. It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation."). The testimony regarding the state of the art up till the time Amgen's patent issued and the experiments performed by Dr. Heartlein show that more than routine experimentation would be required to combine prior art techniques to purify and make EPO that is therapeutically effective in treating human diseases such as anemia.

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entire patent lacks reliable confirmation that he did what he claimed. As discussed earlier in the context of the enablement of Amgen's patent, however, it is not necessary that a disclosed invention actually have been made or even actually attempted. *See Donahue*, 766 F.2d at 534; *Chugai*, 927 F.2d at 1213. Instead, "what is necessary is that [the patentee] provide a disclosure sufficient to enable one skilled in the art to carry out the invention." *Id.* (internal citations omitted). Nothing in the case relied on by Amgen, *In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973), suggests the contrary. *Id.* at 543 (deeming reference insufficient because it stated that attempts to prepare the claimed compounds were not successful); *Donahue*, 766 F.2d at 532 (explaining in that *In re Wiggins* does not support the view that an invention needs to have been actually attempted or made in order to be enabling under section 102(b)). Although in the context of anticipation these arguments may have relevance, *see, e.g.*, *W.L. Gore & Assocs., Inc.* v. *Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983), here, they do not.

(2) Conclusion

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not work. *Genentech*, 108 F.3d at 1366. "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification," *id.*, expert witnesses for both sides were shocked at the lack of direction and detail in Sugimoto's patent. *See Wands*, 858 F.2d at 738; *Enzo*, 188 F.3d at 1374. Dr. Green called the patent "a parody of a scientific document" because "[i]t has very, very poorly constructed experiments for examples. It has absence of controls or defective controls. It has many ambiguities, or worse, implausible statements that are not justified by any evidence. In short, it is a thoroughly unacceptable document from the scientific point of view . . . ." Green Test., R. Trial Tr. at 401: 8-14; *id.* at 506: 5-7. Dr. Erslev, *HMR/TKT's* expert, was similarly "flabbergasted" by Sugimoto's patent. Erslev Test., Trial Tr. at 1754: 24-1755: 9. Like in *Genentech*, here "the claimed invention is the application of an unpredictable technology in the early stages of development." 108 F.3d at 1367. As such, the specification must provide skilled artisans with "specific and useful teaching" and "supply the novel aspects of an invention." *Id.* at 1368, 1366. It is not sufficient merely to set forth a "plan or invitation for those of skill in the art to experiment" without providing sufficient guidance as to how to reproduce the starting materials, to select the hybrid cells, and then, most importantly, to purify the EPO so that it can be used, as is stated in the specification, to treat human diseases such as anemia. *Enzo*, 188 F.3d at 1374.

Like in *Chugai*, here a substantial discovery is claimed, yet there is no credible evidence that the claimed EPO can be purified and produced by skilled artisans by the disclosed process. Indeed, all evidence—even that from HMR/TKT itself—is to the contrary. *Chugai*, 927 F.2d at 1217 (basing

decision on same criteria).[132] Therefore, this Court concludes that Amgen has proved by a fair preponderance of the evidence that Sugimoto's claims were not adequately enabled. As a consequence, Sugimoto does not anticipate any of the asserted claims of the '422 and '080 patents.

b. *Obviousness:* Does Sugimoto Render Obvious Any of the Asserted Claims of the '422, '080, '698, and '349 Patents?

A patent is invalid under 35 U.S.C. § 103 if the differences between the patented subject matter and the prior art are small enough that the patented subject matter "as a whole" would have been obvious at the time of the invention to a person having ordinary skill in the art. 35 U.S.C. § 103 (2001); *SIBIA Neurosciences, Inc.* v. *Cadus Pharm. Corp.*, 225 F.3d 1349, 1355 (Fed. Cir. 2000). Obviousness is determined based on four factual considerations and a set of secondary objective considerations. The factual considerations that are important are (1) the content of the prior art and its scope; (2) the differences that exist between the claimed invention and the

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[132] HMR/TKT makes one last effort to show enablement by arguing that Amgen itself recognized Sugimoto's enablement by identifying Sugimoto as an EPO-producing cell line in its patents. *See, e.g.*, HMR/TKT's Response to Amgen's Proposed Conclusions of Law and Findings of Fact at 10. This argument is baseless. In Amgen's patents and the prosecution history, Amgen merely repeats what Sugimoto *reported* to have done. *See, e.g.*, '933 Patent, Ex. 1, col. 7: 24-35; '933 Patent File History, Ex. 2034, at 237. This type of reporting is part of an inventor's duty to recount assertions in prior art as Dr. Lin testified. Lin Test., R. Trial Tr. at 587: 18-588: 23. Further, that Amgen tried to procure the cells from Sugimoto does not show that Amgen believed Sugimoto's experiments to be successful, but instead that it was trying to obtain the starting materials—if indeed they were obtainable—so that it could attempt to verify that which Sugimoto claims. Lastly, Amgen told the PTO that Sugimoto did not suggest or teach recombinant procedures involving cloning the EPO gene. 10/3/86 Amendment, Ex. 2001, at 250. This last argument therefore fails.

prior art; (3) the level of skill in the prior art (as opposed to that in the claimed invention); and (4) the "objective indicia of non-obviousness." *Yamanouchi Pharm. Co., Ltd.* v. *Danbury Pharm., Inc.*, 231 F.3d 1339, 1342 (Fed. Cir. 2000); *see also Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Ruiz* v. *A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000).

The "objective indicia of non-obviousness," referred to as secondary considerations, include (1) commercial success; (2) copying; (3) long-felt, but unresolved need; (4) the failure of others; (5) commercial success; (6) unexpected result created by claimed inventions; (7) unexpected properties of the claimed inventions; (8) licenses revealing industry respect for the invention; and (9) skepticism of skilled artisans before the invention. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Although they are "but a part of the 'totality of the evidence' that is used to reach the ultimate conclusion of obviousness," *Richardson-Vicks, Inc.* v. *Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997), these secondary considerations are by no means secondary in importance. *Ryko Mfg. Co.* v. *Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991); *Arkie Lures, Inc.* v. *Gene Larew Tackle, Inc.*, 119 F.3d 953, 958 (Fed. Cir. 1997) (emphasizing that the secondary considerations are not secondary). To the contrary, they "can constitute 'highly probative, objective criteria fully capable of serving as a foundation for the legal conclusion of unobviousness.'" *Perkin-Elmer Corp.* v. *Computervision Corp.*, 732 F.2d 888, 895-96 (Fed. Cir. 1984) (quoting *Raytheon Co.* v. *Roper Corp.*, 724 F.2d 951, 961 (Fed. Cir. 1983)). More than that, "secondary considerations may often be the *most probative* and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Ruiz*, 234 F.3d at 668 (quoting *Stratoflex Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)) (internal quotation marks omitted) (emphasis added).

Importantly, the defense of obviousness can be based on a single prior art reference or more than one prior art reference. In other words, if it is shown that it would have been obvious to one skilled in the art to modify the teachings of a reference or combine the teachings of more than one reference to accomplish the claimed invention, then the patent for the claimed invention is invalid. *SIBIA Neurosciences*, 225 F.3d at 1356; *Richardson-Vicks*, 122 F.3d at 1483. To prevail, however, the alleged infringer must meet two requirements. First, it must show a suggestion, teaching or motivation to modify the reference or combine the prior art references. *Yamanouchi*, 231 F.3d at 1341 (citing *In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985)); *Brown & Williamson Tobacco Corp.* v. *Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000) (quoting *C.R. Bard, Inc.* v. *M3 Systems Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998)); *Ortho Pharm. Corp.* v. *Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992).[133] This may be inferred from the prior art, from knowledge of one skilled in the art, or from the nature of the problem to be solved. *Brown & Williamson Tobacco*, 229 F.3d at 1125 (citing *Pro-Mold & Tool Co.* v. *Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996)). Broad conclusory statements, standing alone, are insufficient, however. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000). Instead, evidence of motivation or suggestion to modify a reference or

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[133] The Federal Circuit has stressed the importance of this showing:

> [V]irtually all [inventions] are combinations of old elements. . . . Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. . . . To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Rouffet, 149 F.3d at 1357-58 (internal quotations and citations omitted).

combine it must be "clear and particular." *Dembiczak*, 175 F.3d at 999; *see Brown & Williamson Tobacco*, 229 F.3d at 1125. Second, it must show that one of ordinary skill in the art would reasonably expect that so combining or modifying the prior art references would achieve success. *Id.*

(1) Claim 1 of the '422 Patent and Claims 2-4 of the '080 Patent

HMR/TKT argues that Sugimoto afforded the skilled worker a reasonable expectation of success in obtaining the claimed invention of the asserted claims of the '422 and '080 patents because Sugimoto discloses on its face every specific element of those claims, except for the extra 166th amino acid. HMR/TKT's Reply Br. After Trial at 10. In other words, it urges, that *because* Sugimoto discloses all the elements of the asserted claims, it necessarily shows that those skilled in the art would have had a reasonable expectation of success in practicing Amgen's claimed invention. This, however, erroneously conflates into a single issue what the Federal Circuit has defined as a two-part inquiry. *See, e.g.*, *Brown & Williamson Tobacco*, 229 F.3d at 1124; *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Also, it fails to address the four factors involved in the obviousness inquiry. *Cf. Ruiz*, 234 F.3d at 660, 664 (vacating and remanding district court's judgment for failure to address and make specific findings on the four factors outlined in *Graham*). Although it may appear today, with the benefit of hindsight, that Sugimoto's patent renders the asserted claims of the '080 and '422 patents obvious, as will be explained below, the record shows that at the time Amgen's patents issued there was no reasonable expectation of success in modifying Sugimoto and doing that which Amgen did. Indeed, what Amgen did was anything but obvious when considered in light of the secondary factors. *See Dembiczak*, 175 F.3d at 999 (stressing the importance of "casting the mind back to the time of the invention" and ignoring the "powerful attraction of hindsight-based obviousness").

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

HMR/TKT contends that Sugimoto alone, along with what was known by those skilled in the art, renders obvious the asserted claims of the '422 and '080 patents. As stated in *Amgen I*, Sugimoto itself "suggested combining its invention with prior art sources relating to both purification and therapeutic delivery." *Amgen I*, 126 F. Supp. 2d at 114 n.29. Thus, there was motivation to combine Sugimoto and prior art to make EPO to treat patients suffering from diseases such as anemia.

The differences between Sugimoto (combined with prior art knowledge) and claim 1 of the '422 patent and the asserted claims of the '080 patent, however, can be summarized easily.

Sugimoto does suggest all that is contained in claim 1 of the '422 patent. Amgen contends that Sugimoto does not disclose "therapeutically effective" because it does not use those words nor describe an increase in hematocrit. While this argument may indeed have merit in an anticipation analysis, where more complete detail and description may be required, it fails here. Sugimoto suggests (if not teaches) EPO that is therapeutically effective when it claims that its EPO is useful in the treatment of patient diseases such as anemia. Sugimoto Patent, Ex. 2229, col. 3: 66-4: 2; *see also* Kingston Test., Trial Tr. at 1227, 1234. Moreover, it is undisputed that Sugimoto claims it produced human EPO in excess of 1000 units/10 (6) cells, a range HMR/TKT asserts, and Amgen does not dispute, to be therapeutically effective. Sugimoto Patent, Ex. 2229, col. 6: 27-39. Amgen argues in defense that Sugimoto does not suggest purification *from mammalian cells grown in culture* specifically. The Federal Circuit made clear in *Amgen II*, however, that when considering obviousness with respect to the '422 and '080 product claims, "a claimed

product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations." *Amgen II*, 314 F.3d at 1354 n.20 (citing *General Electric Co.* v. *Wabash Corp.*, 314 U.S. 364, 373 (1938), and *Cochrane* v. *Badishce Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884)). Therefore, this argument fails.

There are more differences between Sugimoto and the asserted claims of the '080 patent than there are between Sugimoto and claim 1 of the '422 patent. As the Court explained in *Amgen I*, claims 2, 3, and 4 (by dependency) make reference to the mature erythropoietin amino acid sequence of Figure 6, which is unique to and at the heart of Amgen's invention. Sugimoto does not discuss in any way the amino acid sequence of human EPO. HMR/TKT assumes that because Sugimoto discloses human EPO, it necessarily discloses human EPO with either a 165 amino acid sequence or 166 amino acid sequence. HMR/TKT's Reply Br. After Trial at 12. This, however, is not necessarily true. As Amgen points out, Reply to HMR/TKT's Findings of Fact ¶ 149, this Court already found that changes at the C-terminus neither affect the biological activity of the protein nor inhibit proper secretion from the cells. *Amgen I*, 126 F. Supp. 2d at 133 (concluding that the absence of the 166th amino acid is not significant because the absence of the last four amino acids does not substantially change the glycoprotein). Moreover, HMR/TKT does not dispute that EPO fragments, rather than human EPO, can elicit an erythropoietic response in the Cotes bioassay. *See* Jean-Paul Boissel et al., *Erythropoietin Structure-Function Relationships*, 268 J. Biol. Chem. 15883 (1993), Ex. 2302, at 15983-93 (showing that variants of human EPO with internal deletions are biologically active, as measured in bioassays). Thus, simply because human cells were used does not necessarily mean that the sequence was present.

Amgen also claims, correctly, that Sugimoto does not examine the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, a limitation found in claims 2 and 3 of the '080 patent. While this argument supports a finding that Sugimoto does not anticipate these claims, it does not work here in an obviousness inquiry. As discussed above, Sugimoto claimed its EPO was "advantageously useable . . . . in the prevention or treatment of human diseases such as anaemia" Sugimoto Patent, Ex. 2229, at col. 3: 66-4: 2. This necessarily suggests an increase in reticulocytes and red blood cells since, as Dr. Schumacher explained and Amgen did not dispute, these side affects necessarily coincide with therapeutically effective treatment. Schumacher Test., R. Trial Tr. at 824-25.

(b) Level of Ordinary Skill in the Art[134] and Reasonable Expectation of Success

This Court has already found that those skilled in the art at the time Sugimoto patented his invention would not have been able to use Sugimoto—along with knowledge and skill in the art—to select the hybrids or purify the EPO without undue experimentation. HMR/TKT does not suggest that at the time that Amgen made its claims—as opposed to the time that Sugimoto filed its patent—common knowledge in the art about these procedures had advanced. Moreover, there is no

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[134] HMR/TKT contends and Amgen does not dispute that in this action, "a person of ordinarily skill in the art of the patents-in-suit in 1983-84 would have been a scientist with a Ph.D. or M.D. in the biological, biochemical or medical sciences, working in research at the time and having at least two years of post-doctoral research experience in protein production, glycoslyation, and purification, and in the preparation and clinical evaluation of protein-based pharmaceutical compositions for use in human therapy." HMR/TKT's Proposed Conclusions of Law ¶ 80; Amgen's Responsive Conclusions of Law (accepting by not refuting this assertion); *see also* Kingston Test., R. Trial Tr. at 128: 12-14 (agreeing that one skilled in the filed of molecular and cell biology "would be somebody who has a PhD and roughly two years of experience working in the area").

proof on record—aside from that discussed and rejected—that those skilled in the art would have been capable of practicing Sugimoto let alone practicing Amgen's claimed invention based on Sugimoto and general knowledge of skilled artisans. Indeed, there is proof to the contrary. No one has ever purified EPO from non-recombinant cells to substantial homogeneity and all attempts to obtain a therapeutic result had failed. Although a particular reference need not be enabling to be considered in the obviousness inquiry, the asserted combination (here Sugimoto combined with knowledge of one skilled in the art) must provide a reasonable expectation of successfully practicing the claimed invention. *Boehringer Ingelheim Vetmedica, Inc.* v. *Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003); *Yamanouchi*, 231 F.3d at 1343; *Beckman Instruments, Inc.* v. *LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make or use the apparatus or method.").[135] It is with respect to this part of the

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[135] Although both parties agree that the Federal Circuit in *Amgen II* stated that a reference need not be enabling to be considered prior art when analyzing obviousness, they disagree as to the extent that a non-enabled prior art may be considered. Amgen argues that it is only that which the non-enabled art actually teaches that can be considered. *See, e.g.*, Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶¶ 215, 216 (arguing that "to render obvious the asserted prior art must enable ordinarily skilled artisans to make and use the claimed invention" and citing *Beckman Instruments*, 892 F.2d at 1551 and *In re Payne*, 606 F.2d 303, 314 (C.C.P.A. 1979) in support). HMR/TKT argues, on the other hand, that the Federal Circuit said in *Amgen II* that a non-enabled reference is relevant to the analysis for all the art it "discloses" and, therefore, argues that anything disclosed in the prior art is fair game.

A review of the case law does not provide a definitive answer but indicates that although a reference need not be enabled to be prior art, the reference when combined with other references or common knowledge of ordinarily skilled artisans at the time of the obviousness inquiry should enable the claimed invention, that is, place it in possession of the public.

analysis that HMR/TKT has failed to carry its burden. It has failed to show by clear and convincing evidence that one skilled in the art could practice Amgen's claimed invention with a reasonable expectation of success. Further, the evidence attested to by multiple experts that Sugimoto's experiments lacked sufficient controls, were not confirmed, and were unbelievable suggests that those of ordinary skill in the art would actually not *reasonably* expect that combining Sugimoto with knowledge of skilled artisans would achieve success. *Brown & Williamson Tobacco*, 229 F.3d at 1125.

(c) Secondary Considerations

As discussed in great detail in *Amgen I*, 126 F. Supp. 2d at 115-16, this is definitely a case where the secondary considerations weigh heavily into the Court's decision. Indeed, here they represent the "most probative and cogent evidence in the record." *Ruiz*, 234 F.3d at 668 (quoting *Stratoflex*, 713 F.2d at 1538). Before Amgen's path-breaking invention, there was a long-felt need for the mass production of EPO. *Amgen I*, 126

"If not, every otherwise anticipating reference that is proved to be non-enabling would automatically render the claim obvious, despite not teaching ordinarily skilled artisans how to make and use the invention." Amgen's Reply to HMR/TKT's Proposed Findings of Fact ¶ 216. Arguably, if the non-enabled reference can be combined with other references or knowledge of those skilled in the art such that the combination teaches how to make and use the now claimed invention then it should render the claim obvious. In other words, if by the time the claimed invention is patented, the skill in the art or other references that have been suggested have filled in the missing blanks from the non-enabled reference, then the claimed invention should be rendered obvious. On the other hand, if the missing blanks are still missing (or the non-enabled reference does not suggest the right combination of other references) then the non-enabled reference should not be able to render the claimed invention obvious. In sum, although a prior art reference need not be enabled to render a claimed invention obvious, enablement is not wholly irrelevant. As discussed above, here, the missing blanks were still missing when Amgen filed its patents, and HMR/TKT has not shown a reasonable expectation of success on the part of skilled artisans.

F. Supp. 2d at 108. Many skilled artisans tried unsuccessfully to achieve Dr. Lin's inventions. *Id.* at 115-16. If Sugimoto's invention truly rendered Amgen's invention obvious, one wonders why so many tried and failed. *See Panduit Corp.* v. *Dennison Mfg. Co.*, 774 F.2d 1082, 1099 (Fed. Cir. 1985) ("That many others including [the alleged infringers] had tried for years and failed to create the [claimed invention] is virtually irrefutable evidence that the [claimed invention] would not have been obvious to those skilled in the art when it was invented."), *judgment vacated on other grounds*, 475 U.S. 809 (1986), *on remand*, 810 F.2d 1561 (Fed. Cir. 1987). Importantly, it was Amgen's invention that opened the floodgates for EPO production and led to the first pharmaceutical composition containing EPO to obtain FDA approval. *Amgen I*, 126 F. Supp. 2d at 116. It was Amgen that won the lucrative race to make human EPO suitable for treatment of chronic anemia. *Id.*

HMR/TKT argues, however, that Amgen did not explain to which claims its success was attributable, and that the mapping of the EPO gene was claimed in Dr. Lin's '008 patent. HMR/TKT's Response to Amgen's Proposed Findings of Fact ¶46. In support, it cites *Riverwood International Corp.* v. *Mead Corp.*, 212 F.3d 1365, 1367 (Fed. Cir. 2000) (citing *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). In *Riverwood* and *GPAC*, however, success was attributable to factors that were entirely outside the scope of the claims. This is not the case here. The evidence suggests that these patents were groundbreaking in their own right since, as discussed above, no one had been able, even using Sugimoto, to purify to homogeneity EPO (as claimed in the '422 patent)[136] or to

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[136] This Court interpreted "purified from mammalian cells grown in culture" to mean purified to substantial homogeneity. *Amgen I*, 126 F. Supp. at 89. It found, however, the evidence was insufficient to warrant the conclusion that plasma EPO could be purified to homogeneity via the prior art. *Id.* at 115.

produce a product that was actually therapeutically effective (as claimed in the '422 and '080 patents).

(2) Claims 4-9 of the '698 Patent and Claims 1, 3, 4, 6, and 7 of the '349 Patent

HMR/TKT contends that every element of the asserted claims of the '698 and '349 patents is found in Sugimoto except the 166th amino acid of Figure 6, the "non-human" or non-EPO promoter or transcription control sequences and the amplified marker DNA. HMR/TKT's Opening Br. After Trial at 41-44. The missing elements, it argues, were available and routinely used in the art in 1983-84. Specifically, it asserts that

> [g]iven the teachings of Sugimoto, it would have been obvious for the ordinary skilled worker to use retroviral insertion to operatively link a retroviral promoter and its transcription control sequences to the erythropoietin production genetic sites in a kidney or liver tumor cell that produced EPO and to transfer those production sites . . . with an amplifiable marker DNA if desired, to a lymphoblastoid cell.

Id. at 41-42. HMR/TKT, however, fails to show a suggestion or motivation to modify the teachings of Sugimoto to create what Amgen claims. Moreover, it has not shown with clear and convincing evidence that one of skill in the art would have had a reasonable expectation of success in achieving Amgen's '349 or '698 claimed inventions using such techniques. Finally, as they did in the context of the '080 and '422 claims, the secondary factors weigh heavily in Amgen's favor on the issue.

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

Sugimoto differs from the asserted claims of the '349 patent in that it does not disclose the "non-human" or non-

EPO promoter or transcription control sequences as claimed in the asserted claims of the '349 patent. Sugimoto differs from the asserted claims of the '698 patent in that it does not disclose the amino acid sequence of Figure 6,[137] amplified marker DNA, the "dihydrofolate reductase (DHFR) gene DNA," or use of a non-EPO promoter operatively linked to the EPO gene.[138]

With respect to amplified marker DNA, HMR/TKT asserts that Sugimoto's claimed hybrid cells comprise amplified DNA because they have more copies of the EPO gene than are found in normal cells. HMR/TKT Proposed Findings of Fact at 94. Dr. Lodish testified, however, that amplified EPO DNA refers to an increase in the "number of copies of EPO DNA relative to *other* DNA sequences in the genome."

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[137] *See* discussion *supra* regarding Figure 6 and obviousness of the '080 and '422 patents.

[138] HMR/TKT argues that the "non-human" or "other than human" limitations of the asserted patent claims cannot save them from invalidation, because they are source or process limitations. HMR/TKT's Opening Br. After Trial at 42. As HMR/TKT admits, however, there are other "missing elements" from Sugimoto's patent, like transcription control sequences, the amino acid sequence found in Figure 6, amplified marker DNA, the DHFR gene, and operative linkage to the EPO gene. These differences, as will be discussed further below, are determinative notwithstanding the "non-human" or "other than human" limitations. Therefore, the Court declines to address this argument as it relates to these patents. That being said, it is not altogether clear that source or process limitations are irrelevant when considering process claims, as opposed to product claims. *See, e.g.*, *In re Luck*, 476 F.2d 650, 653 (C.C.P.A. 1973) (noting in the product-by-process claim context that process limitations can in certain situations distinguish the product over prior art); *In re Moeller*, 117 F.2d 565, 568 (C.C.P.A. 1941) (same). Moreover, the Federal Circuit did not state that a claimed process could not be rendered patentable solely by the addition of source or process limitations, but instead stated that this was the case for a "claimed product" and a claimed composition. *See Amgen II*, 314 F.3d at 1354 n.20 (making clear that the rule applied to patents that address "a claimed *product*"); *id.* at 1356 (noting that source limitations cannot impart novelty to old compositions).

Lodish Test., R. Trial Tr. at 1099: 25-1100: 1 (emphasis added); *see also* James Darnell, Harvey Lodish & David Baltimore, *Molecular Cell Biology* (1st ed. 1986), Ex. 2394, at 457 ("When mammalian cells are grown in culture, *specific sites* on their DNA can become amplified." (emphasis added)); *id.* at 461 (showing in a diagram that DHFR gene copy numbers increase, but does not depict a change in the chromosome copy numbers). As HMR/TKT admits, Sugimoto's claimed hybrid cells had potentially 4 copies of every gene on every chromosome (two from each parental cell). *See, e.g.*, HMR/TKT's Proposed Findings of Fact at 94; Kingston Test., R. Trial Tr. at 98: 19-99: 5. This does not represent an increase in the relative amount of EPO DNA compared to other DNA sequences.

Notwithstanding this, HMR/TKT argues that Dr. Lodish's testimony regarding amplification supports its argument that Sugimoto's hybrid cells will often have more than four copies of the EPO gene. *See, e.g.*, HMR/TKT's Proposed Findings of Fact at 94 (citing Lodish Test., Trial Tr. at 160: 24-161: 10, 494: 24-495: 3). The Court, however, is not convinced that Dr. Lodish's testimony supports this conclusion. Instead, it appears that in the testimony on which HMR/TKT relies, Dr. Lodish was addressing selection for amplification events using the DHRF gene as a selectable marker—a feature totally missing from Sugimioto.

With respect to the other missing elements, including amplification, HMR/TKT argues that they were available and routinely used in the art in 1983-84. *See, e.g.*, HMR/TKT's Opening Br. After Trial at 41. Instead of focusing on the invention as a whole, however, as required under 35 U.S.C. § 103, HMR/TKT approaches the obviousness inquiry on a piecemeal basis, arguing that the separate elements of Amgen's invention existed in the prior art and, separately, "could" have been done easily. *See, e.g.*, HMR/TKT's Opening Br. at 43-44; HMR/TKT's Proposed Findings of Fact

After Trial at 93-115. "[A]bsent some teaching or suggestion, in the prior art, to combine the elements," however, this is "insufficient." *Arkie Lures*, 119 F.3d at 957; *see also Ruiz*, 234 F.3d at 665; *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosure in the prior art to deprecate the claimed invention."); *Connell* v. *Sears, Roebuck & Co.*, 722 F.2d 1542, 1549 (Fed. Cir. 1983). As the Federal Circuit has explained, "[t]hat all elements of an invention may have been old (the normal situation), or some old and some new, or all new, is however, simply irrelevant. Virtually all inventions are combinations and virtually all are combinations of old elements." *Environmental Designs, Ltd.* v. *Union Oil Co. of California*, 713 F.2d 693, 698 (Fed. Cir. 1983).

HMR/TKT tries to hang its hat on the statements in Sugimoto regarding genetic sites and recombinant techniques. *See* Sugimoto Patent, Ex. 2229, col. 1: 55-2: 3. It argues that Sugimoto's reference to "genetic recombination techniques" suggests combining Sugimoto with retroviral insertion art, that is, that Sugimoto suggested the insertion of non-human transcription control sequences. HMR/TKT's Reply Br. at 13. The Court is not convinced. Sugimoto nowhere suggests using "retroviral insertion" to induce expression of EPO. That the specification specifically defines recombination techniques as those "using DNA ligase, nuclease and DNA polymerase," Sugimoto Patent, Ex. 2229, col. 2: 2-3, argues against interpreting a suggestion of retroviral insertion. Similarly, both Dr. Lodish and Dr. Green testified that an ordinarily skilled artisan reading Sugimoto would not have interpreted the section relied on by HMR/TKT as teaching a way to make cells capable of producing human EPO by recombinant DNA techniques. Lodish Test., R. Trial Tr. at 281: 10-282: 4, 285: 6-23; Green Test., R. Trial Tr. at 405: 19-409: 6. While Dr. Kingston testified that the most commonly used technology to increase expression of the EPO gene in 1983-84 was retroviral insertion, Kingston Test., R.

Trial Tr. at 99: 14-23, when asked how Sugimoto teaches recombinant DNA techniques to increase expression of the EPO coating region, he stated that Sugimoto did so by using "ligases and nucleases and polymerases," *id.* at 104: 14-19—not retroviral insertion.

Moreover, it is not as if "retroviral insertion" was a commonly understood technique that could simply be applied by any skilled artisan in 1983-84. Instead, as Dr. Kingston explained, a skilled artisan would have to rely on many different prior art references to achieve it. *See* Kingston Test., R. Trial Tr. at 99-112 (relying on at least six other references in combination in forming opinion about process of inserting a retrovirus and producing erythropoietin from the resulting cell). That all of these references, save one, were published after Sugimoto's patent issued (after 1983) also supports the conclusion that Sugimoto was not suggesting a combination with retroviral insertion. *See* John M. Coffin, Stephen H. Hughes & Harold E. Varmus, *Retroviruses* (1997), Ex. 2481; Roger D. Cone & Richard C. Mulligan, *High-efficiency Gene Transfer Into Mammalian Cells*, 81 Proc. Nat'l Acad. Sci. 6349 (1984), Ex. 2479; Randal J. Kaufman & Phillip A. Sharp, *Amplification and Expression of Sequences Cotransfected with a Modular Dihydrofolate Reductase Complementary DNA Gene*, 159 J. Molecular Biol. 601 (1982), Ex. 2239; David L. Nelson et al., *Metaphase Chromosome Transfer of Introduced Selectable Markers*, 2 J. Molecular & Applied Genetics 563 (1984), Ex. 2476; Munehisa Ueno et al., *Enhanced Erythropoietin Secretion in Hepatoblastoma Cells in Response to Hypoxia*, 257 Am. J. Physiology C743 (1989), Ex. 2480; John H. Weis et al., *Eukaryotic Chromosome Transfer*, 81 Proc. Nat'l Acad. Sci. 4879 (1984), Ex. 2477.

While the motivation to modify can be found outside the reference itself, *SIBIA Neurosciences*, 225 F.3d at 1358, HMR/TKT has not shown that the knowledge of those skilled in the art or the nature of the problem to be solved suggested

this modification. It is undisputed that the later published retroviral insertion references cited by Dr. Kingston do not refer to Sugimoto or to the expression of EPO or any protein that uses a host cell's gene. *See id.* The only reference that discusses expression of an endogenous gene after insertion of a retrovirus is the Weis article, but that article is not about *increasing* the expression of H-2 antigens as compared to starting cells and did not involve using retroviral insertions to identify cells that produce enhanced amounts of a protein that is either expressed in very small quantities or not at all. Weis et al., *supra*, Ex. 2477, at 4879-83 (identifying that the point of the paper is to transfer the chromosomes to cells of other species). Thus, HMR/TKT has failed to prove the existence of a "clear and particular" suggestion to modify Sugimoto or combine it with prior art so as to produce the asserted claims. *Dembiczak*, 175 F.3d at 999 (noting that while the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability must be "clear and particular"); *id.* (explaining that "[t]he range of sources available does not diminish the requirement for actual evidence" of a motivation or suggestion); *see Brown & Williamson Tobacco*, 229 F.3d at 1125 (same); *SIBIA Neurosciences*, 225 F.3d at 1356 (making clear that the suggestion to combine or modify must be proven, even when a claim of obviousness is based on a single prior art reference); *Rouffet*, 149 F.3d at 1357-58.

HMR/TKT fails to show a suggestion to modify Sugimoto or combine it with prior art with respect to amplification as well. With respect to claims 6, 7, and 8, HMR/TKT merely asserts that although Sugimoto does not disclose or teach a means to position a selection marker such as DHFR next to the EPO gene, it renders this element of the claim obvious because "it was well-known in 1983-84 that the DHFR marker gene can be used to transfer and amplify co-transferred DNA sequences when transfected into CHO cells." HMR/TKT's Proposed Findings of Fact ¶ 448; HMR/TKT's Response to

Amgen's Proposed Findings ¶ 40; HMR/TKT's Reply Br. After Trial at 15. While HMR/TKT may have something with respect to this element, fatally, it neither identified any motivation or suggestion to combine this supposed common knowledge with Sugimoto nor demonstrated how this motivation can be found in the prior art or the problem to be solved. HMR/TKT's Proposed Findings of Fact ¶¶ 448, 452. Given that HMR/TKT shoulders the burden here, this lack of evidence and argument is fatal.

(b) Level of Ordinary Skill in the Art and Reasonable Expectation of Success

Even if one could glean the motivation to modify Sugimoto by applying knowledge in the art to create the claimed invention, HMR/TKT would not prevail here. HMR/TKT has not shown that a skilled artisan would reasonably expect to have succeeded in achieving Dr. Lin's claimed '349 or '698 inventions using such known techniques.[139] As mentioned earlier, HMR/TKT parses elements that comprise one limitation. For example, in its Proposed Findings of Fact, it separates the element "comprising promoter DNA, other than human EPO promoter DNA, operatively linked" from the element "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6." In doing so, it fails to recognize the import of the combination of elements. As this Court pointed out in *Amgen I*, in the context of the '349 patent and tumor cell references, the identity of the sequence of the DNA encoding human erythropoietin was critical. *Amgen I*, 126 F. Supp. 2d at 114-15. Without it, an ordinarily skilled artisan would not have been able to hook up transcription control

[139] Indeed, the only experimental evidence on record attempting to do what Dr. Kingston described by way of Sugimoto and the prior art failed. As HMR/TKT put it in its 5/10/00 trial brief, "Amgen's Dr. Browne failed completely when he attempted to transfect cells with viral promoters to increase their production of EPO." Amgen's App. to Mot. for Judgment re '349, Tab E (HMR/TKT's 5/10/00 Trial Br.), at 22.

sequences in a way that caused transcription of the EPO gene, or to obtain cells with the specified structures. *Id.* Like the prior art tumor cell references, Sugimoto does not speak to the genetic characteristics of the cells, and HMR/TKT has not shown during either trial that any knowledge possessed by those of ordinary skill in the art in 1983-84 could fill this gap.[140] *Id.* This reasoning equally applies to the '698 patent's "promoter DNA other than human erythropoietin DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" (claim 4) and "amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" (claims 6 and 9).[141]

Moreover, the Court does not overlook the fact that HMR/TKT's only evidence on this issue comes from testimony by Dr. Kingston, who earlier testified that a person of ordinary skill in the art, applying Dr. Lin's specification—which includes the identification of the EPO gene sequence, splice, donor, and restriction sites, and much more detail than Sugimoto's patent—would not have been able to produce EPO using a cell's endogenous EPO gene. Kingston Test., R. Trial Tr. at 116: 23-117: 24 (testifying that an ordinarily skilled worker could not have taken Lin's teaching to insert randomly a retrovirus into a cell and to obtain an EPO-producing cell with a reasonable likelihood of success). His testimony that ordinarily skilled artisans could have combined Sugimoto with references regarding retroviral insertion

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[140] Importantly, the Weis et al. article, discussed above, studied a gene that had already been cloned, and therefore the researchers were able to confirm the structure of the mouse DNA that had been inserted into hamster cells, using Southern blotting techniques. Weis et al., *supra*, Ex. 2477, at 4881-82, Fig. 3.

[141] This reasoning also applies to claims 5, 7, 8, and 9, as they are dependant on the other claims. *Cf. Fine*, 837 F.2d at 1076 ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious.").

is seemingly incongruous, Kingston Test., R. Trial Tr. at 100: 11-101: 19; 116: 11-16; 117: 15-24, not to mention inconsistent with yet other testimony by the doctor. In the first trial, Dr. Kingston stated that before Dr. Lin cloned the EPO gene, it would not have been obvious for one skilled in the art to do what he did. Kingston Test., Trial Tr. at 1357: 11-1358: 12 (explaining why he retracted yet another inconsistent statement). The Court does not, therefore, lend Dr. Kingston's oscillatory testimony on this issue much weight—especially when considered in light of Dr. Green's and Dr. Lodish's testimony that one skilled in the art, lacking knowledge of EPO's DNA sequence, would not have had a reasonable expectation of successfully making EPO-producing cells by genetic recombination. Green Test., R. Trial Tr. at 406: 17-22; 409: 3-6 (explaining that in order to use any of the recombinant methods mentioned in Sugimoto, "you must know the sequence of the erythropoietin gene and that information . . . did not become available until Dr. Lin's inventions"); Lodish Test., R. Trial Tr. at 285: 21-23. Indeed, Dr. Kingston implicitly admitted the importance of knowing EPO's DNA sequence when he testified that the first step in genetic recombination is to isolate the EPO-neo fragment, which suggests that the gene must first have been cloned. Kingston Test., R. Trial Tr. at 103: 17-104: 18 (using Demonstrative Exhibit TX II W as support for conclusion that Sugimoto teaches this type of genetic recombination); Demonstrative Ex. TX II W.[142]

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[142] HMR/TKT argues as it did with the '080 and '422 patents that the cloning and isolation of EPO is the subject of Lin's original '008 patent, and thus cannot save the patents in issue here. In other words, HMR/TKT argues that because Amgen first reported its discovery of the genetic sequence of EPO in the '008 patent, reference to the genetic sequence can simply be ignored in the obviousness inquiry concerning all other patents. The Court disagrees. First, HMR/TKT offers no legal support for this contention. Second, the genetic sequence of EPO is at the heart of these patents. Simply because the sequence specifically is not a novel addition

Thus, HMR/TKT has failed to prove that skilled artisans, without knowing EPO's DNA sequence, would reasonably expect that combining Sugimoto with prior art references regarding retro viral insertion and knowledge regarding amplification would successfully achieve what Amgen claims.

(c) Secondary Considerations

As with the claims of the '422 and '080 patent, the secondary considerations play a large role in the Court's decision with respect to obviousness. For the reasons discussed above and in *Amgen I*, 126 F. Supp. 2d at 116, the Court finds that the secondary factors strongly counsel it against a finding of obviousness. The real world story in evidence here not only reflects the inadequacy of the prior art, but compels a conclusion of nonobviousness of the claimed inventions in suit. *See Panduit*, 774 F.2d at 1099.

(3) Conclusion

Having considered the scope and content of the prior art references, the differences between such references and the claimed inventions, how one skilled in the art might combine such references in order to make what Amgen claimed, and the objective secondary considerations, the Court concludes the HMR/TKT has failed to persuade the Court by clear and convincing evidence that the asserted claims of the '080, '422, '349, and '698, patents were obvious in light of Sugimoto and the prior art.

B. Goldwasser[143]

1. Background

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as compared to *Amgen's* other patents does not render it obvious in light of *Sugimoto's* patent.

[143] HMR/TKT does not contend that Goldwasser anticipates the asserted claims of the '080, '349, or '698 patents or renders obvious any of the asserted claims of the '698 or '349 patents. *See, e.g.*, HMR/TKT's Opening Br. After Trial [Doc. No. 808] at i.-iii.

a. Overview of Goldwasser

Dr. Goldwasser obtained a preparation of highly purified erythropoietin derived from human urine i.e., it was naturally-occurring EPO. *Amgen I*, 126 F. Supp. 2d at 111.[144] From 1979 to 1981, Drs. Goldwasser and Baron conducted a clinical study in which approximately 10,000 units of the human urinary EPO—in doses of 500 and 1000 units—were administered to three anemic patients. Ex. 2057, at A 196399; Erslev Test., Trial Tr. At 1579; *Amgen I*, 126 F. Supp. 2d at 111. Dr. Goldwasser reported a number of effects in the patients: an increase in reticulocyte count in all three patients, an increase in erythroid cells in the marrow and an increased plasma iron clearance rate in two patients, and an increase in red cell mass in at least one patient. *Id.* Expert testimony by Dr. Erslev explained that these effects are "strong evidence for an increase in the rate of red cell production." *Amgen I*, 126 F. Supp. 2d at 112. Hematocrit levels, however, were unchanged. *Id.* As a result, Dr. Goldwasser admits that his abortive, three-patient trial was a failure. *Id.* at 112.

b. The Court's Holdings in *Amgen I*[145]

(1) Anticipation

In *Amgen I*, the Court held that Dr. Goldwasser's study did not anticipate the asserted claims in the '422 and '080 patents, because the accepted standard by which physicians measure a therapeutic response to EPO is an increase in hematocrit, and Dr. Goldwasser admitted that "there was no significant change in hematocrit in any patient" and that the trial was a failure. *Amgen I*, 126 F. Supp. at 112. The Court interpreted Amgen's claims to require a therapeutically effec-

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[144] Dr. Goldwasser's work does not pertain to cells that have been altered by recombinant means. *Amgen I*, 126 F. Supp. 2d at 113.

[145] The history of patents that are no longer at issue is not included below. For that information, *see Amgen I*, 126 F. Supp. 2d at 112-14, and *Amgen II*, 314 F.3d at 1352-53.

tive amount of EPO—one that provides a sustained increase in hematocrit. Thus, it held that Dr. Goldwasser's study "falls far short of anticipating" the pharmaceutical composition claims of the '080 and '422 patents. *Id.* at 112. Because claims 2 and 3 of the '080 patent required actual production of red blood cells as well as reticulocytes, the Court also held that Goldwasser did not anticipate these claims. *Id.* at 112.

Further, the Court pointed to other differences between Goldwasser's study and Amgen's claims. First, the Court stated that Amgen specifically excluded urinary EPO preparations from the scope of the claims by including the claim limitations "non-naturally occurring" and "not isolated from human urine." Thus, it concluded that claims 2 and 3 of the '080 patent do not encompass Goldwasser's urinary EPO treatment. *Id.* at 112. Second, Goldwasser's study does not involve cells that have been altered by recombinant means, and therefore, it held that none of the '349 claims are implicated. *Id.*

(2) Obviousness

The Court held that because Dr. Goldwasser's study was a failure and a person skilled in the art "would not reasonably have expected that Dr. Goldwasser's work would eventually bear fruit," none of Amgen's patents were invalid for obviousness. *Amgen I*, 126 F. Supp 2d at 114. The Court also found, *inter alia*, that HMR/TKT "failed to prove the existence of any suggestion in the prior art to combine [Essers or Goldwasser and Yanagawa or Chiba] so as to produce the pharmaceutical compositions claimed in the . . . '080, and '422 patents." *Id.* It explained that "the fact that no one has ever—then or now—attempted to determine if a pharmaceutical composition comprising human EPO could be made from these cultured prior art cells also informs the Court's decision." *Id.* Therefore, the Court stated that "the contention that these various references could be combined to produce a pharmaceutical composition meeting the limitations of . . .

claim 4 of the '080 patent and claim 1 of the 422 patent is simply unsubstantiated conjecture." *Id.* Lastly, the Court stated that the secondary considerations counseled strongly against a finding of obviousness. Thus, at the close of HMR/TKT's defensive case, the Court granted Amgen's 52(c) motion for judgment of validity with respect to the defense of obviousness.

c. The Federal Circuit's Opinion

HMR/TKT challenged, on appeal, the Court's acceptance of Goldwasser's assertion that his test was a failure in light of the testimony of Dr. Baron, Goldwasser's collaborator. *Amgen II*, 314 F.3d at 1352-3. Dr. Baron reported to the FDA in 1984 that stimulation of erythoid marrow was detected. *Id.* Specifically, HMR/TKT pointed out that the Court failed to look to the specification to define therapeutic effect. The Federal Circuit agreed and stated that the term "therapeutically effective" must be construed in accordance with *Markman* v. *Westview Instruments* before the issue of anticipation and obviousness could be resolved. Therefore, it vacated and remanded for further proceedings with respect to Goldwasser. *Amgen II*, 314 F.3d at 1353.[146]

2. The Claims at Issue

On remand, HMR/TKT argues that Goldwasser anticipates claim 1 of the '422 patent and renders obvious claim 1 of the '422 patent and claims 2-4 of the '080 patent.[147] The relevant claims are as follows:

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[146] As the Court has discussed above, this procedure promotes comity and collegiality among the Federal Circuit and the district courts.

[147] HMR/TKT does not contend that Goldwasser anticipates the asserted claims of the '080, '349, and '698 patents or renders obvious any of the asserted claims of the '698 or '349 patents. *See, e.g.*, HMR/TKT's Opening Br. After Trial at i.-iii.

> *'422 Claim 1*: A pharmaceutical composition comprising a *therapeutically effective amount* of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, where in said erythropoietin is purified from mammalian cells grown in culture.

'422 Patent, Ex. 1, col. 38: 36-41 (emphasis added).

> *'080 Claim 2*: An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

'080 Patent, Ex. 1, col. 38: 39-44.

> *'080 Claim 3*: A non-naturally occurring erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

'080 Patent, Ex. 1, col. 38: 45-50.

> *'080 Claim 4*: A pharmaceutical composition comprising a *therapeutically effective amount* of an erythropoietin glycoprotein product according to Claim 1, 2 or 3.

'080 Patent, Ex. 1, at col. 38: 51-53 (emphasis added).

3. Discussion

a. Anticipation

(1) Claim 1 of the '422 Patent

Given the Court's construction of the term "therapeutically effective," a critical factor in the anticipation analysis is whether any of the effects elicited by Goldwasser actually, in and of themselves, helped to heal or cure the class of patients

listed in column 33 of the specification.[148] Therefore, the Court will review, in turn, the responses elicited by Goldwasser—and asserted by HMR/TKT to be "therapeutically effective."[149]

(a) Increase in Reticulocytes

HMR/TKT argues that a "therapeutically effective amount" of EPO encompasses an amount that results in an increase in reticulocyte count, whether or not there is an increase in hematocrit, because this increase, in and of itself, helps to heal or cure anemia. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 28-31. In support, it explains that reticulocytes function like normal red blood cells and deliver greater amounts of oxygen to the body's tissues than do older red blood cells. *Id.* The increased oxygen delivery to the tissues, it asserts, "confers health benefits on the patient—it can help to resolve anemia and possibly prevent strokes and heart attacks." *Id.* In support of this contention, it relies mainly on the testimony of Drs. Schumacher and Foster. *Id.*

HMR/TKT overemphasizes the relative significance of reticulocytes in the oxygenation of the body's tissue. Experts

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[148] Amgen also argues that Goldwasser does not disclose the limitation "purified from mammalian cells grown in culture." HMR/TKT argues that this is a source or process limitation that the Federal Circuit specifically pointed out could not save claim 1 from invalidation in an anticipation analysis. The Court need not address the issue since, as will be shown below, the evidence shows that Goldwasser did not disclose EPO that is "therapeutically effective."

[149] HMR/TKT did not argue specifically that an increase in erythroid cells in the marrow signifies a therapeutic response. HMR/TKT's Proposed Findings of Fact at 6-14 (contending that reticulocytes, ferokinetics and erythrocyte-mass change (i.e., red cell mass change) are measures of therapeutic efficacy). Presumably, this is because erythroid marrow stimulation means the marrow is stimulated to raise the reticulocytes. Schumacher Test., R. Trial Tr. at 17-25. Therefore, any argument about erythroid cells in the marrow would necessarily be included in an argument about reticulocytes.

from both sides agree that reticulocytes comprise only one percent of all red blood cells. Schumacher Test., R. Trial Tr. at 829: 18-20; Erslev Test., Trial Tr. at 1685: 5-7. They exist for about three days, whereas *mature* red blood cells exist for 100-120 days. Erslev Test., Trial Tr. at 1684: 21-1685: 7. Moreover, no expert testified that a transitory increase in reticulocytes meaningfully elevates the oxygen levels of the body as a whole. Dr. Schumacher did not testify that a mere increase in reticulocytes increases oxygen supply to these tissues. Instead, she carefully testified that "if you are increasing the oxygen supply," there would be a reduction in the risk of stroke or heart attacks. Schumacher Test., R. Trial Tr. at 813-14 (emphasis added).[150] Both Drs. Erslev and Eschbach testified that reticulocytes are not the accepted reference standard for oxygenation of the body as a whole; that is, recticulocyte counts do not provide direct evidence of the number of red blood cells in circulation and do not always reflect the amount of red blood cells in the body. Erselv Test., Trial Tr. at 1687: 14-1689: 7; Eschbach Test., R. Trial Tr. at 653: 6-14 (stating that the number of circulating red blood cells is determined by the hematocrit).[151] This is because measurements of reticulocytes only reflect the production of red blood cells—not the destruction. Erslev Test., Trial Tr. at 1687: 14-1689: 7; Eschbach Test., R. Trial Tr. at 662-64, 670: 8-10. Reticulocytes do not account for the rate of red cell loss, which could exceed the rate of production. As explained by Dr. Eschbach, reticulocytes may never mature into red

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[150] The Court also notes that HMR/TKT produced no evidence that heart attack or stroke were risks associated with the diseases listed in the specification or that a reduction in the risk of stroke or heart attacks helps to heal or cure the diseased states listed in the specification.

[151] This is consistent with the Court's findings in *Amgen I*, that "[b]y increasing and maintaining the patient's hematocrit to normal or near normal levels, the ability of the patient's blood to provide a steady supply of sufficient oxygen to body tissues can be restored." 126 F. Supp. 2d at 99.

blood cells, because of intervening factors such as iron deficiency, infection, inflamation, blood loss, or rapid red cell destruction. Eschbach Test., R. Trial Tr. at 662-64; 670: 21-25.[152]

Perhaps most telling is the fact that experts from both sides agreed that an increase in reticulocytes is merely an *indication* or "surrogate marker" that a therapeutic effect, i.e., one that actually helps to heal or one that makes the patient feel better, is going to follow. *See, e.g.*, Foster Test., R. Trial Tr. at 965: 3-7 (describing an increase in reticulocytes as a "surrogate marker" of activity and of therapeutic effect); Schumacher Test., R. Trial Tr. at 807: 3-5 (testifying that increase in reticulocytes is "the first indication of a therapeutic response"; *id.* at 813: 3-18 ("[T]he reticulocyte response is the *first response that gives you a clue* that you're getting a response from your therapy . . . the *early harbinger* of the cure or treatment." (emphasis added)); Eschbach Test., R. Trial Tr. at 766: 4-17 (agreeing that an increase in reticulocytes puts a physician "on the lookout for the hematocrit to rise"); *id.* at 660: 22-661: 8, 669: 10-670: 2; Christensen Test., R. Trial Tr. at 1186: 9-24 (testifying that reticulocytes

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[152] Dr. Eschbach illustrated his point with an analogy to a bathtub. Eschbach Test., R. Trial Tr. at 662-64. The Court borrows the analogy to provide background here. Consider a bathtub: the water is the level of hematocrit, the spigot spits out reticulocytes (the early red blood cells), and the drain is the cell destruction or loss. Hematocrit is measured by the amount of red cells produced and by the number of red cells destroyed. In a patient suffering from renal failure, many times the hematocrit drops because red cell destruction exceeds the rate at which red cells are being produced. When EPO stimulation is started, it is as if the spigot has been turned on, increasing the amount of reticulocytes flowing into the tub. Eventually, the tub may start to fill, but there is no guarantee that it will, because the drain is not completely plugged. Iron deficiency, infection, inflammation, or blood loss could prevent the reticulocytes from maturing or could destroy red blood cells. Therefore, simply measuring what is coming out of the spigot and not taking into account what is going down the drain is not sufficient.

are a "marker . . . that the marrow is putting out more blood cells," which "signals that there will ultimately be [a benefit]"); *id.* at 1185: 1-17. That Amgen administered more EPO to those patients that showed an increase in reticulocytes and ferrokinetics and told the FDA that *"[t]he first evidence of a response* to three times weekly . . . administration of EPOGEN® is an increase in the reticulocyte count within ten days," *Physicians' Desk Reference* (56th ed. 2002), Ex. 2497, at 582 (describing Amgen's EPOGEN product) (emphasis added), merely supports the point made by HMR/TKT's own witnesses: an increase in reticulocytes is an indicator or marker that an increase in hematocrit will follow.

The bulk of the testimony indicates that an increase in reticulocytes alone does not help patients feel better. Indeed, HMR/TKT's Dr. Erslev conceded that only by increasing and maintaining hematocrit is the patient able to gain energy and feel better. Erslev Test., Trial Tr. at 1681: 18-1683: 2. Even HMR/TKT's Dr. Foster—a pharmacist arguably not qualified to testify in the area—admitted after a series of direct questions from the Court that an increase in reticulocytes such as that exemplified in Goldwasser would not in and of itself help patients feel better. Foster Test., R. Trial Tr. at 964-66.

HMR/TKT places a great deal of weight on Dr. Ohls' testimony regarding the anemia of prematurity. She testified that an increase in reticulocytes is typically accompanied by an improvement in an infant's overall condition that does not necessarily correspond to an increase in hematocrit, and that clinical signs that an infant is doing better as a result of EPO therapy can occur even with a decrease in hematocrit. Ohls Test., R. Trial Tr. at 1020-21 (noting that conditions like tachycardia, apnea, and poor weight gain improve with an increase in reticulocytes, even if the hematocrit stays the same or decreases); *id.* at 1025. While this testimony may seem at first glance to support HMR/TKT's case on this

point, after a careful review of the testimony of Dr. Ohls and her mentor, Dr. Christensen, it is clear that it does not.

Importantly, Dr. Ohls carefully qualified her testimony by stating that the clinical signs of anemia "*gradually* disappear" after a moderate increase in reticulocytes. *Id.* at 1021: 2-4 (emphasis added); *see also* Christensen Test., R. Trial Tr. at 1185: 1-17 (pointing out that Dr. Ohls said "gradually," and explaining that a rise in reticulocyte count, in and of itself, has "no medical meaning," except to "help you predict that eventually this baby is going to have a hematocrit that is stable"). Dr. Ohls' testimony is further qualified by the biological facts associated with babies and anemia. As Dr. Ohls explained, babies, unlike adults, are constantly growing. As they grow, their blood volume also constantly grows in proportion to their size. Ohls Test., R. Trial Tr. at 1022: 9-21. While, in adults, one can measure the percentage of red blood cells in a sampled blood cell volume to get an accurate reading of hematocrit,[153] in babies, hematocrit is a constantly moving target, because as babies grow their blood volume increases. *Id.*; *see also* Christensen Test., R. Trial Tr. at 1184: 7-15 (noting that an infant's growth rate complicates the measuring of hematocrit). Therefore, even an actual increase in red cell *mass* (versus just an increase in reticulocytes) can result in a constant or even decreased hematocrit. Ohls Test., R. Trial Tr. at 1024.[154] Moreover, Dr. Ohls stated that a neonatologist would use reticulocytes to measure EPO's efficiency—not because it necessarily had a therapeutic effect —but because it "means that the EPO is working to stimulate the bone marrow to make new red blood cells." *Id.* at 1026; *see also id.* at 1029: 20-23 ("But in general, when we treat these babies with EPO they start making new reticulocytes,

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[153] Hematocrit is the ratio of the red-cell mass to the total blood volume.

[154] For an explanatory depiction, see Ohls' Demonstrative Ex. 4.

new red blood cells; they stimulate the circulation, build up the red-cell mass, the hematocrit."). As discussed above, however, just because a person's body is making new red blood cells does not mean that it is doing so fast enough to make up for continuing destruction of red blood cells. Presumably, this is why Dr. Ohls and her peers, in their clinical research, measure the hematocrit, the amount of blood drawn out for laboratory evaluation, and the number of transfusions and the volume of transfusions the babies receive in addition to the reticulocyte count. *Id.* at 1040-41, 1043: 21-24.[155]

The significance of Dr. Ohls' testimony is further diminished by the testimony of her mentor, Dr. Christensen. He stated repeatedly that the reticulocyte count, in and of itself, does not have any effect on the baby and does not help the baby in any way. *Id.* at 1183: 15-22, 1185: 1-17, 1186: 6-24. Instead it is merely a biological indicator that a benefit will ultimately follow. *Id.* Further, he clarified that an infant's growth rate does not invalidate hematocrit as a measure of therapeutic efficacy. *Id.* at 1183: 23-1184: 15. Instead, a physician has to consider the growth factor in infants much like a physician takes into account an adult patient's age, sex,

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[155] Indeed, in the cited studies regarding anemia of prematurity, hematocrit was always measured. Darlene A. Calhoun et al., *Consistent Approaches to Procedures and Practices in Neonatal Hematology*, 27 Clinics in Perinatology 733 (2000), Ex. 252, at 734-35 (basing decision to use transfusions solely on hematocrit); Robin K. Ohls et al., *Effects of Early Erythropoietin Therapy on the Transfusion Requirements of Preterm-Infants Below 1250 Grams Birth Weight: A Multicenter, Randomized, Controlled Trial*, 108 Pediatrics 934 (2001), Ex. 253, at 934 (abstract) (measuring hematocrit and concluding that EPO should not be used in infants under 1250 grams birth weight, because it did not prevent use of transfusions); Robin K. Ohls & Robert D. Christensen, *Recombinant Erythropoietin Compared with Erythrocyte Transfusion in the Treatment of Anemia of Prematurity*, 119 J. Pediatrics 781 (1991), Ex. 2507, at 781 (measuring hematocrit and concluding that EPO offers promise as an alternative to transfusion in neonates with anemia of prematurity).

disease state, etc., in order to understand the meaning of the patient's hematocrit. *Id.* Dr. Christensen made clear that EPO is used to stabilize an infant's hematocrit and to prevent it from falling to a level that would require a transfusion. Christensen Test., R. Trial Tr. at 1189: 23-1190: 4.

In further support of the conclusion that reticulocytes in and of themselves do not help to heal or cure babies suffering from anemia is the fact that a decision whether to transfuse a baby (the goal of using EPO on infants is to avoid the necessity of a transfusion)[156] is never based on reticulocytes alone. *Id.* at 1116-17. Evidently, the reticulocytes can be high and the hematocrit low, and in that situation, the baby will still need the transfusion.

In light of Dr. Christensen's testimony and the other testimony discussed above regarding reticulocytes in adults, Dr. Ohls' testimony is unpersuasive. Although, as Dr. Schumacher testified, "therapeutic response" may be "related to the reticulocytes response," Schumacher Test., R. Trial Tr. at 811: 11-12, the evidence does not show that a reticulocyte response, in and of itself, helps to heal or cure patients suffering from anemia or from any of the other diseases listed in column 33 of the specification.

For these reasons, after a careful review of all the evidence, this Court finds that an increase in reticulocytes alone does not in and of itself help to heal or cure a patient suffering from anemia or any of the diseases listed in the specification.

(b) Increase in Plasma Iron Clearance Rate (i.e., Ferrokinetics)

HMR/TKT next contends that increases in the plasma iron clearance rate are an indication that red blood cell production

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[156] Both Dr. Christensen and Dr. Ohls agreed that the goal of using EPO in infants with anemia prematurity is to avoid transfusions. Ohls Test., R. Trial Tr. at 1027: 7-10; Christensen Test., R. Trial Tr. at 1200: 7-21.

has increased and that there is a therapeutic response to EPO. HMR/TKT's Proposed Findings of Fact ¶ 51.[157] As with reticulocytes, however, HMR/TKT has failed to show that an increase in plasma iron clearance rate is "therapeutically effective."

First, an increase in the plasma iron clearance rate indicates an increase in reticulocytes, but not necessarily an increase in red blood cell mass. As discussed above, there are a number of intervening events, such as cell death and destruction, which preclude one from concluding that the reticulocytes become red blood cells. *See, e.g.*, Eschbach Test., R. Trial Tr. at 670: 3-25 (noting that ferrokinetics only reflect red blood cell production, not destruction); *id.* at 658: 2-8.

Second, Dr. Eschbach testified that ferrokinetic measurements were understood to be a biological effect that did not guarantee that a therapeutic response would follow. Eschbach R. Trial Tr. at 660: 22-661: 8; *id.* at 658: 2-8 ("Ferrokinetics is an investigational tool. It does not . . . tell you anything about therapeutic response.").

Third, Dr. Schumacher admitted that inferences as to the rate of red blood cell production cannot be drawn from the plasma iron disappearance rate without also measuring the plasma iron concentration (serum iron) at the beginning and the end of the trial. Schumacher Test., R. Trial Tr. at 835: 17-836: 9, 837: 4-21; Eschbach Test., R. Trial Tr. at 689: 13-691: 20, 693: 21-25; Allan J. Erslev, *Anemia of Chronic Renal Failure*, in *Hematology* (3rd ed. 1983), Ex. 249, at 399. Although the plasma concentration was measured at the be

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[157] When red blood cells are produced, iron in the blood plasma clears into the bone marrow. Schumacher Test., R. Trial Tr. at 805. The rate of clearance of iron from the plasma is known as the plasma iron clearance rate. *Id.*; Eschbach Test., R. Trial Tr. at 693: 4-11. For further explanation, see Eschbach Test., R. Trial Tr. at 689-91.

ginning of the Goldwasser study, it was not measured at the end. Schumacher Test., R. Trial Tr. at 841: 24-842: 2.

Because HMR/TKT points to no other persuasive evidence on the point,[158] the Court finds that it has failed to prove that an increase in the plasma iron clearance rate, in and of itself, helps to heal or cure anemia or any of the diseases referred to in column 33 of the specification.

(c) Erythrocite (Red Cell) Mass Changes

An increase in erythrocite mass, i.e., an increase in red cell mass, is an increase in the number of erythrocytes. That is, it reflects an increase in the aggregate number of red blood cells. Schumacher Test., R. Trial Tr. at 896: 16-897: 10. HMR/TKT argues that Dr. Eschbach testified that erythrocite mass change is a measure of therapeutic efficacy because increasing the number of red cells helps to heal or cure anemia. HMR/TKT's Findings of Fact at 13. It omits, however, Dr. Eschbach's clear qualification that this is true only if "there's *significant* mass changes." Eschbach Test., R. Trial Tr. at 658: 13-15. He explained that when erythrocyte mass changes are *of sufficient quantity*, they elicit a therapeutic effect because they represent an increase in hematocrit. *Id.* at 660: 1-5.

Here, HMR/TKT does not produce any evidence that the red cell mass changes were significant or meaningful. Indeed, arguably it cannot prove such a thing. Dr. Eschbach's testimony, undisputed by any of the expert witnesses, that a significant increase in erythrocyte mass is the same as an increase in hematocrit prevents HMR/TKT from so proving,

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[158] HMR/TKT has made other arguments in support of its contention, most of which center on the literature. The Court, however, has not found any of these arguments persuasive, given Amgen's more than adequate counter-arguments. *See, e.g.*, HMR/TKT's Proposed Findings of Fact ¶¶ 52-60; Amgen's Response to HMR/TKT's Proposed Findings of Fact ¶¶ 24-29.

because the Court has already found and the Federal Circuit has affirmed that there was no significant increase in hematocrit in any of the patients. Thus, there could be no significant increase in red cell mass.

For that matter, given that the red cell mass changes only occurred in one patient and were not shown to be significant, the evidence does not support a finding that Goldwasser's EPO actually elicited red cell mass increases.[159]

Further, HMR/TKT did not prove that a larger dose of Goldwasser's EPO would have increased red cell mass, increased hematocrit, or elicited a therapeutic response. While there is some evidence in HMR/TKT's favor, the bulk of it suggests the contrary.

First, Dr. Baron himself attempted to increase the dosage and the duration with patient #3, and still there was no recorded increase in hematocrit above the baseline level at any time during or after the study. Indeed, the opposite occurred; as HMR/TKT's expert attested, the patient's red cell mass declined over the treatment period. Goldwasser Data, Ex. 242, at AM 47 038668 (patient #3); Schumacher Test., R. Trial Tr. 885: 14-886: 20; *id.* at 887: 1-5; Eschbach Test., R. Trial Tr. at 759: 6-17 (testifying that there was no significant increase in hematocrit for any of the three patients); 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007 (explaining to the FDA that the third patient received a trial of the medication using an altered protocol that increased the dosage and length of time).[160]

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[159] This is consistent with the Court's finding in *Amgen I* that "actual production of mature red blood cells was not achieved." *Amgen I*, 126 F. Supp. 2d at 112.

[160] HMR/TKT argues that Dr. Baron did not extend the duration long enough, since he only administered the medicine for three weeks. *See, e.g.*, Schmumacher Test., R. Trial Tr. at 894: 13-15. It points to Dr. Baron's letter to the FDA, which stated that "one needs to give larger

Second, although HMR/TKT presented evidence that the experimentors did not believe the EPO was toxic or impure, *see, e.g.*, IND Application for EPO, Ex. 2489, at HMR 935380, 935344; 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007, there is contrary evidence that Goldwasser's EPO was unsuitable for increased dosages. Eschbach Test., R. Trial Tr. at 706: 1-16 (testifying that it was impure and toxic), IND Application for EPO, Ex. 2489, at HMR 935386. Dr. Eschbach even opined that, given these issues with the Goldwasser preparation, the international review boards likely would not have permitted Goldwasser to give more of his urinary EPO preparation to human subjects even had he wanted to, Eschbach Test., R. Trial Tr. at 705: 20-706: 16, and that skilled artisans would likely refrain from giving it to patients in larger dosages for longer duration. *Id.* at 704: 22-23, 705: 22-706: 16; IND Application for EPO, Ex. 2489, at HMR 935386.

Although HRM/TKT's expert, Dr. Schumacher testified that had Goldwasser's EPO been continued in a larger dose, an increase in hematocrit would have been seen, Schumacher Test., R. Trial Tr. at 894: 12-15, Dr. Eschbach testified that the results would not have been different had a larger dose

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doses than initially anticipated and for more prolonged periods of time to achieve the substantial and lasting stimulation of red cell production." 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007. It also points to testimony by Drs. Schumacher and Eschbach and to Amgen's product literature, which claim that a rise in hematocrit usually occurs within two to six weeks. Schumacher Test., R. Trial Tr. at 894: 12-16; Eschbach Test., R. Trial Tr. at 725: 12-21; *Physicians' Desk Reference* (56th ed. 2002), Ex. 2497, at 582. Notwithstanding this, Dr. Eschbach testified that an effective EPO therapy would have produced immediate and dramatic increases in hematocrit. Eschbach Test., R. Trial Tr. at 679: 8-680: 14. Further, even if the Court agreed with HMR/TKT on this specific issue, as discussed above, the evidence simply does not show that an increased dosage would necessarily have lead to therapeutic effectiveness. Here, the red cell mass of the patient that received the altered protocol actually decreased.

been given to the patients over a longer period of time, because of the potential problems with the EPO. Eschbach Test., R. Trial Tr. at 770: 24-771: 6 (explaining that after he received the EPO T ½ values and became aware of the fragments and marked decrease in EPO clearance rate, he doubted whether giving more EPO would make any difference, and believed it might even be harmful); *id.* at 730-31 (same); *id.* at 704-706; *cf.* 2/6/84 Baron Letter to National Center for Drugs and Biologics, Ex. 2058, at A 199034 (describing the increase in reticulocytes as only "mild to modest").

Third, given the incentives to continue the study, the fact that the experimentors themselves chose to abandon it and considered it a failure indicates that an increase in dosage or length of administration would not have led to success. Goldwasser Dep. at 317: 14-321: 2;[161] *cf. Fromson* v. *Advance Offset Plate, Inc.*, 755 F.2d 1549, 1558 (Fed. Cir. 1985) ("[A]nother's experiment, imperfect and never perfected[,] will not serve as an anticipation or as part of the prior art, for it has not served to enrich it." (quoting *Picard* v. *United States Aircraft Corp.*, 128 F.2d 632, 635 (2nd Cir. 1942) (internal quotation marks omitted)).

Thus, HMR/TKT failed to prove that Goldwasser's EPO would have achieved therapeutic effectiveness had Goldwasser continued his experiment. The mere possibility of success is not enough to save HMR/TKT. *Cf. Continental Can Co. USA, Inc.* v. *Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991) (stating in the context of anticipation that "[t]he mere fact that a certain thing *may* result from a given set of circumstances is not sufficient," and explaining that the

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[161] HMR/TKT tries to soften the impact of this testimony by arguing that Goldwasser was hired as a consultant by Amgen in 1981. The study, however, was not discontinued until 1988. IND Application for EPO, Ex. 2489, at HMR 935313. Therefore, HMR/TKT has not shown a causal link between the consultancy and the discontinuation.

disclosure must "show that the natural result flowing from the operation as taught would result in the performance of the questioned function").

(2) Conclusion

HMR/TKT contends that all three of the elicited responses discussed above are "surrogate markers of therapeutic efficacy of EPO because each of them represents a critical step in the development of erythroctyes." HMR/TKT's Proposed Findings of Fact ¶¶ 64-66. This specific contention, however, belies its argument. That these three responses are but surrogate markers or indicators that a therapeutic response is on the way necessarily indicates that they did not, in and of themselves, elicit a therapeutic response. This is consistent with this Court's reading of Amgen's specification (discussed in the claim construction part of this memorandum and opinion). These biological responses are critical steps, precursory responses, before a therapeutic result is achieved. Because Goldwasser's study did nothing more than elicit these biological effects or surrogate markers, experts from both sides agreed that there was no evidence that Goldwasser's urinary EPO clinically improved the condition of any of the patients. *See, e.g.*, Means Test., Trial Tr. at 1918: 16-1919: 12 (admitting that there is no evidence that the patients benefitted from any purported activity and labeling the activity as biologic effects); Eschbach Test., R. Trial Test. at 676: 7-18.

In sum, HMR/TKT failed to prove by clear and convincing evidence that Goldwasser anticipates claim 1 of the '422 patent.

b. Obviousness

HMR/TKT argues that Goldwasser alone renders claim 1 of the '422 patent and claims 2-4 of the '080 patent obvious.

(1) Claim 1 of the '422 Patent and Claims 2- 4 of the '080 Patent

(a) Scope and Content of the Prior Art/ Differences Between the Claimed Invention and the Prior Art

Goldwasser differs from claim 1 of the '422 patent in that, as discussed above, it does not disclose EPO that is therapeutically effective or purified from mammalian cells grown in culture. Goldwasser differs from claims 2-4 of the '080 patent in that it does not disclose the mature amino acid sequence of Figure 6[162] or EPO isolated from a source other than human urine.[163] Moreover, claims 2-4 of the '080 patent

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[162] For the significance of this difference, see the discussion of whether Sugimoto renders these claims obviousness.

[163] With respect to "purified from mammalian cells grown in culture" and "not isolated from human urine," the Federal Circuit made clear that a finding of non-obviousness cannot be rendered solely on source or process limitations. *Amgen II*, 314 F.3d at 1354 n.20. Amgen, however, argues not simply that these source or process limitations save the claims in their own right, but that because of these source and process differences, Goldwasser's urinary EPO actually differs in structure and function from Dr. Lin's recombinant EPO because of its source. *See, e.g.*, Amgen's Post-Trial Br. at 33-38. Specifically, it claims that EPO molecules derived from Dr. Lin's cell cultures differ in glycosylation, degradation, clearance rates, in vivo potency, and therapeutic effect. *See, e.g.*, Amgen's Proposed Findings of Fact ¶¶ 69-83. While these differences may be significant, Amgen fails to point to convincing case law recognizing unclaimed product attributes as differences in this part of the analysis. *See, e.g.*, *Graham*, 383 U.S. at 17-18 (noting that an obviousness determination is based in part on differences between the prior art and the "claims"); *Riverwood Int'l Corp.* v. *Mead Corp.*, 212 F.3d 1365, 1366 (Fed. Cir. 2000) (noting that an obvious determination is based in part on "the differences between the prior art and the *claims*" (emphasis added)). That being said, one of the secondary factors recognized by the Federal Circuit is "unexpected properties." *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997) ("[U]nexpected properties can show that a claimed compound that appeared to be obvious on structural grounds was not obvious when looked at as a whole."); *see Rouffet*, 149 F.3d at 1355. Arguably, then, these contentions may be relevant to that part of the analysis. The Court,

require production not just of reticulocytes, but also of red blood cells. Although one patient in Goldwasser showed an increase in red cell mass, the Court has found these increases neither significant nor meaningful—not only because the increases were not substantial enough to increase hematocrit, but also because the results occurred in only one patient. Thus, the Court found, as it did in *Amgen I*, that actual production of mature red blood cells was not evidenced. Lastly, claim 4 of the '080 patent, like claim 1 of the '422 patent, requires therapeutic effectiveness, but the Court has found Goldwasser's EPO is not therapeutically effective.

(b) Level of Ordinary Skill in the Art and Reasonable Expectation of Success

In terms of claim 1 of the '422 patent and claim 4 of the '080 patent, HMR/TKT has not shown that one of ordinary skill in the art had a reasonable expectation of success in obtaining EPO compositions that achieved therapeutic effectiveness. Although HMR/TKT tried to show that it was simply a matter of increasing the length and amount of the dosage, it has not convinced the Court.[164] HMR/TKT provides no other support for its defense.

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however, does not rely on them here, as the many other secondary factors already explicated support a holding of non-obviousness.

[164] Indeed, there is evidence suggesting that it would not have been possible to give increased amounts of the Goldwasser EPO to patients. In a letter to the FDA, Goldwasser made clear that the supply was limited and that preparing more was a painstaking task. 7/7/80 Baron Letter to FDA, Ex. 2056, at A 193007; see also 8/17/79 Application for Continuation Grant, Ex. 250, at A 196293 (explaining that the supply of EPO is small and the study was contingent on obtaining more); IND Application for EPO, Ex. 2489, at HMR 935313 (requesting in 1988 that the IND be put on inactive status, as the researchers "do not have sufficient supplies of the drug available to carry on anticipated studies at this time and for the immediate foreseeable future").

With respect to claims 2-3 of the '080 patent, the evidence once again fails to show a reasonable expectation of success in achieving an increase in the production of red blood cells. The one patient that did receive the increased dosages showed a decrease, not an increase, in red blood cell mass. HMR/TKT has produced no further evidence to support its contentions.

(c) Secondary Considerations

Even if HMR/TKT had shown a reasonable expectation of success on the part of one skilled in the art to practice the claimed invention, this Court would still conclude that HMR/TKT has failed to show by clear and convincing evidence that Goldwasser rendered the claims obvious. This is because the secondary considerations counsel strongly against a finding of obviousness, just as they did in the context of Sugimoto. The secondary considerations discussed above with respect to Sugimoto, and explicated in *Amgen I*, apply here. *Amgen I*, 126 F. Supp. 2d at 115-16.

(2) Conclusion

Having considered the scope and content of the prior art, the differences between Goldwasser and the claimed invention, the level of skill in the art, and the objective secondary considerations, the Court holds that HMR/TKT has failed to show by clear and convincing evidence that Goldawsser renders claim 1 of the '422 patent and claims 2-4 of the '080 obvious.

VII. CONCLUSION, DECLARATION, AND ORDER FOR JUDGMENT

As with the first trial, it has been an honor to have presided over this case. The attorneys representing both parties litigated the case with dedication, skill, intelligence, integrity, and patience.

For the reasons set forth above, as a result of the remand trial the Court makes the further declaration:

Claim 1 of the '422 patent is valid.

Claims 2-4 of the '080 patent are valid.

Claims 4-9 of the '698 patent are valid and literally infringed.

Claim 7 of the '349 patent is valid and literally infringed.

SO ORDERED.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE

APPENDIX C

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

CIVIL ACTION NO. 97-10814-WGY

AMGEN, INC.,

Plaintiff,

v.

HOECHST MARION ROUSSEL, INC. and
TRANSKARYOTIC THERAPIES, INC.,

Defendants.

MEMORANDUM AND ORDER

YOUNG, C.J. October 30, 2003

INTRODUCTORY NOTE: On September 18, 2003, this Court held that Amgen had successfully rebutted the presumption of prosecution history estoppel but noted that it might have to revisit the issue if the Federal Circuit's *Festo* opinion was published before this Court's opinion was finished. 9/18/03 Pretrial Conference Tr. at 7, ll. 17-25, and 8, ll. 1-5. This Court had scheduled release of this opinion for early October, 2003, pending final proofreading. The Federal Circuit released its opinion in *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, No. Civ.A.95-1066, 2003 WL 22220526 (Fed. Cir. Sept. 26, 2003) ("*Festo III*") on September 26, 2003. Because *Festo III* authoritatively interprets the Supreme Court's decision in *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722 (2002) ("*Festo II*"), the recent Federal Circuit decision governs here under familiar stare decisis principles.

As this Court's interpretation of the Supreme Court decision had proceeded along a somewhat different tack, and

since the growth of the law in this area "moves at a lightning pace," *Festo III*, 2003 WL 22220526, at *11 (Rader, J., concurring), it seems appropriate to set forth this Court's original analysis of *Festo II*, noting its confirmation or remediation on a section-by-section basis by the Federal Circuit in *Festo III*, and identifying and setting forth the revised analysis required by that decision.

As will be discussed in further detail below, this Court reasserts its prior holding—in light of *Festo III*—that Amgen has successfully rebutted the presumption of prosecution history estoppel. Therefore, its earlier finding that HMR/TKT infringes claims 2 through 4 of U.S. Patent No. 5,621,080 (issued April 15, 1997) (the "'080 patent") is reaffirmed.

I. INTRODUCTION

In light of the recent Supreme Court decision in *Festo II*, 535 U.S. 722, the Federal Circuit remanded to this Court its ruling in *Amgen, Inc.* v. *Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69 (D. Mass. 2001) ("*Amgen I*"), that Amgen, Inc. ("Amgen") was not estopped by the prosecution history from claiming equivalent infringement by the human erythropoietin ("EPO") product ("HMR 4396") produced by Hoechst Marion Roussel, Inc.[1] and Transkaryotic Therapies, Inc. (collectively "HMR/TKT"). *Amgen Inc.* v. *Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1345 (Fed. Cir. 2003) ("*Amgen II*"). Based upon *Festo II*, the Federal Circuit ruled that a presumption of prosecution history estoppel applied here. Therefore, it vacated this Court's finding of equivalent infringement and remanded "for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel" as laid out in *Festo II. Amgen II*, 314 F.3d at 1345. This opinion addresses the discrete issue of whether Amgen

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[1] Hoechst Marion Roussel, Inc. is now known as Aventis Pharmaceuticals, Inc.

has successfully rebutted the *Festo II* presumption of prosecution history estoppel held to be present in *Amgen II*. *Id.*

II. DISCUSSION

A. Background and Procedural History

In *Amgen I*, this Court construed the amendment "mature erythropoietin amino acid sequence of FIG. 6" in claims 2-4 of U.S. Patent No. 5,621,080 (issued April 15, 1997) (the "'080 patent") as requiring an EPO glycoprotein "comprising the fully realized erythropoietin amino acid sequence of Figure 6, which depicts 166 amino acids." *Amgen I*, 126 F. Supp. 2d at 100. Pursuant to this construction, the Court found that HMR 4396 did not literally infringe claims 2, 3, and 4 of the '080 patent because HMR 4396 comprised only 165 amino acids. *Id.* at 101.

This Court then turned to the doctrine of equivalents and found that HMR 4396 performed substantially the same function in substantially the same way to obtain substantially the same result as the EPO glycoprotein of claims 2 and 3 of the '080 patent. *Id.* at 133. Therefore, it ruled that Amgen's '080 patent was equivalently infringed by TKT/HMR's product. *Id.*

In response to TKT/HMR's argument that Amgen should be estopped from arguing equivalent infringement, this Court ruled that prosecution history estoppel did not apply because Amgen did not add the "mature amino acid sequence of Figure 6" limitation "in an attempt to overcome a rejection, to avoid prior art," but, instead, to "demonstrate that 'same invention' type double patenting did not apply," that is, to distinguish the '080 patent from U.S. Patent No. 5,547,933 (the "'933 patent"). *Id.* at 134-35.

The Federal Circuit agreed that the amendment was made for this purpose but made clear that under *Festo II*, "a narrowing amendment to satisfy *any* requirement of the Patent

Act may give rise to an estoppel." *Amgen II*, 314 F.3d at 1345 (emphasis added). Therefore, it held that the presumption of prosecution history estoppel applied here. The Federal Circuit then vacated this Court's finding of equivalent infringement and remanded for an analysis based on the "narrow ways of rebutting the Supreme Court's presumption of estoppel" outlined in *Festo II*. *Id.* at 1345. Because the Court's factual findings (that TKT/HMR's product performed substantially the same function in substantially the same way to obtain substantially the same result) were not disturbed—or even challenged—on appeal, the Court need only analyze whether Amgen can rebut the presumption of prosecution history estoppel and pursue an infringement claim based on the doctrine of equivalents. If Amgen can, the Court's ruling that Amgen's '080 patent was equivalently infringed shall be reaffirmed.

On May 16, 2003, Amgen moved for judgment under the Federal Rule of Civil Procedure 52(c) that claims 2-4 of the '080 patent are equivalently infringed [Document No. 659]. TKT/HMR opposed Amgen's motion and moved for judgment that Amgen is estopped from asserting infringement under the doctrine of equivalents [Document No. 678].[2] Both parties, however, have agreed that the Court summarily can

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[2] TKT/HMR argues that Amgen should not be allowed to pursue a Rule 52(c) motion because Amgen has already presented evidence on the issue of infringement of claims 2-4 of the '080 patent and a Rule 52(c) motion is a vehicle for a party that has not yet presented its evidence. TKT/HMR's Opp'n [Document No. 703] at 1. Here, when TKT/HMR moved for judgment of non-infringement at the close of Amgen's case, the Court decided in TKT/HMR's favor as to literal infringement but denied the motion under the doctrine of equivalents as to the '080 patent. *Amgen I*, 126 F.Supp. 2d at 101 n.22. Thereafter, TKT/HMR presented its rebuttal case on equivalents. Thus, the proper motion is in actuality one for judgment under Rule 52(a), one which the Court can summarily decide without further evidentiary support.

decide this motion based on the current record without further evidentiary presentation. TKT/HMR's Mem. in Opp'n at 1; Amgen's Mem. in Support at 5-6.

B. Overview Of *Festo II* As Interpreted By This Court And The Federal Circuit

The doctrine of equivalents was created because language is not always sufficiently precise to capture the essence, nuances, and range of an invention in light of unexpected technological advances. *Festo II*, 535 U.S. at 731 ("Things are not made for the sake of words, but words for things." (quoting *Autorigo Co. of America* v. *United States*, 384 F.2d 391, 397 (Ct. Cl. 1967)). The doctrine of equivalents was designed to provide patent applicants the wiggle room that claim language alone cannot, thus protecting patentees from copyists who make insubstantial changes. *Festo II*, 535 U.S. at 732-33; *Graver Tank & Mfg. Co.* v. *Linde Air Prods. Co.*, 339 U.S. 605, 607 (1950). In other words, it was designed to protect the intended invention, even if not adequately or ably described.

Prosecution history estoppel, on the other hand, arises when an amendment, by its language, discernibly limits the scope of the invention before the Patent and Trademark Office (the "Patent Office"). The purpose of prosecution history estoppel is to "hold the inventor to the representations made during the application process and the inferences that may reasonably be drawn from the amendment." *Festo II*, 535 U.S. at 737-39.

> The doctrine of equivalents is premised on language's inability to capture the essence of innovation, but a prior application describing the precise element at issue undercuts that premise. In that instance, the prosecution history has established that the inventor turned his attention to the subject matter in question, knew the

> words for both the broader and narrower claim, and affirmatively chose the latter.

Id. at 734-35. Prosecution history estoppel, therefore, takes root in the virtues of public notice and the reduction of uncertainty that is sometimes created by the doctrine of equivalents. Tony Caliendo, *Foreseeable Trouble: How* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. *Offends Fundamental Policies of the U.S. Patent System by Making Prosecution History Estoppel Depend Upon Foreseeability*, 2003 BYU L. Rev. 309, 314 (2003). Competitors "rely on [prosecution history] estoppel to ensure that their own devices will not be found to infringe by equivalence." *Festo II*, 535 U.S. at 727.

An obvious tension exists between the doctrine of equivalents and prosecution history estoppel. The doctrine of equivalents provides protection for more than just the literal claims, but this added protection creates uncertainty. Caliendo, *supra*, at 314. In other words, competitors are not provided notice of the breadth of the patent. Prosecution history estoppel, on the other hand, can provide such certainty and notice. The Supreme Court in *Festo II* tried to balance the competing interests of public notice and protection of patents by rejecting the Federal Circuit's complete bar approach[3] and further defining which amendments give rise to a presumption of estoppel, what equivalents are subsequently barred by such estoppel, and how the "presumption" of estoppel can be overcome. *Festo II*, 535 U.S. at 736-42.

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[3] In *Festo Corp.* v. *Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 243 F.3d 558, 574-75 (2000) ("*Festo I*"), the Federal Circuit held that prosecution history estoppel completely bars the patent applicant from asserting any equivalent to a narrowed element. This Court previously has followed, but criticized, the Federal Circuit's approach. *See Control Resources, Inc.* v. *Delta Electronics, Inc.*, 133 F. Supp. 2d 121 (D. Mass. 2001).

1. How Does The "Presumption" Work?

   a. *The Court's Original Analysis:* The "presumption" of estoppel is not really a presumption at all, but rather a burden-shifting device similar to the "presumption" of patent validity.

The Supreme Court in *Festo II* made clear that a "presumption" of prosecution history estoppel arises when an amendment is made to secure the patent and the amendment narrows its scope. *Festo II*, 535 U.S. at 736. The "presumption," however, does not completely bar the inventor from asserting infringement against any equivalents to the narrowed element. *Id.* at 738-39. The inventor can overcome the "presumption" by showing that the amendment does not surrender the particular equivalent in question. *Id.* at 740. Thus, this "presumption" shifts to the inventor not only the burden of production but also the burden of persuasion to get out from under the "presumption" of prosecution history estoppel outlined in *Festo II*.[4] Once the patentee meets these

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[4] When dealing with a "true" presumption, if the party with the burden presents evidence to rebut the presumed fact, the presumption simply disappears—the "bursting bubble theory." Young, Pollets & Poreda, Mass. Practice Evidence § 301.3 at 119 (2d ed. 1998). Here, however, the patentee does not simply have to present evidence to rebut the "presumption" but actually has to persuade the Court that it did not surrender the equivalent in question. Such imprecision in language is regrettable, for it means that the definition of the word "presumption" is one thing in patent law and quite another in civil rights and employment discrimination cases. *See, e.g.*, *Reeves* v. *Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 142-43 (2000) (noting that once respondent met its burden of production, the presumption disappeared); *St. Mary's Honor Ctr.* v. *Hicks*, 509 U.S. 502, 510 (1993) (stating that the presumption "simply drops out of the picture" once the defendant has succeeded in carrying its burden of production). Usually such imprecision does little more than confuse the bar and raise the already excessive cost of litigation still higher.

In the area of criminal sentencing, however, the judicial embrace of words like "evidence," "finding," and "fact," has the pernicious effect of cloaking an intellectual vacuity with forms of due process that are wholly

burdens, prosecution history estoppel no longer applies and the patentee may allege equivalent infringement of the narrowed element. *Accord Festo III*, 2003 WL 22220526, at *4.

b. *The Federal Circuit's Analysis:* CONFIRMS THIS COURT'S ANALYSIS.

Neither the Federal Circuit nor the Supreme Court addressed whether the "presumption" outlined in *Festo II* is a true presumption. The Federal Circuit's description of the "presumption," however, confirms this Court's analysis. *Festo III*, 2003 WL 22220526, at *4.

2. What Quantum Of Evidence Is Necessary To Rebut The Presumption?

a. *The Court's Original Analysis:* Proof by a fair preponderance of the evidence is sufficient to rebut a "presumption" of prosecution history estoppel.

While the Supreme Court made clear that the burden of overcoming the "presumption" lies with the patentee, it did not define the quantum of evidence necessary to meet such a burden. In other words, the Supreme Court did not lay out whether the patentee must make a showing by a fair preponderance of the evidence, clear and convincing evidence, or some other standard, nor has any other court yet addressed this quandary in a published opinion.[5]

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unwarranted, thus mistakenly propping up a system that today is both morally and intellectually bankrupt. *See United States* v. *Green*, No. 02-10054-WGY (D. Mass. filed Jan. 10, 2002) (forthcoming).

[5] The Supreme Court did note that the burden here was similar to that outlined in *Warner-Jenkinson Co., Inc.* v. *Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), and identical to the approach advocated by the United States as Amicus Curiae. *Festo II*, 535 U.S. at 740. Neither of these two sources, however, specify the quantum of evidence required. In *Warner-Jenkinson*, the Supreme Court merely stated that the burden was on the patent holder to establish the reason for an amendment. 520 U.S. at 33.

Important in determining the requisite standard is the surrounding legal landscape. Here, that landscape—patent litigation concerning both the doctrine of prosecution history estoppel and the doctrine of equivalents—is riddled with uncertainty. *Festo II*, 535 U.S. at 732 ("It is true that the doctrine of equivalents renders the scope of patents less certain."). Nevertheless, the Supreme Court purposely preserved the doctrine of equivalents in *Festo II*; it made clear that there was value to the doctrine. *Festo II*, 535 U.S. at 732 ("Each time the [Supreme] Court has considered the doctrine of equivalents, it has acknowledged this uncertainty as the price of ensuring the appropriate incentives for innovation . . . ."); *Warner-Jenkinson*, 520 U.S. at 28 (reaffirming that the doctrine is a secure part of a patentee's settled rights and stating that it was up to Congress—not the Supreme Court—to discard the doctrine). With this landscape in mind, the Court holds that the standard for overcoming the "presumption" of prosecution history estoppel is proof by a fair preponderance of the evidence[6] for the following reasons.

Instituting anything other than the most familiar standard —a fair preponderance of the evidence—would add yet another layer of uncertainty and cause litigation over prosecution history estoppel to proceed inconsistently. *See* John H. Strong, McCormick on Evidence § 340 (5th ed. 1999) (explaining that the clear and convincing standard "has not

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The United States, in its Amicus Curiae brief, urged the Supreme Court to apply a burden comparable to that of *Warner-Jenkinson*, and stated that this burden entailed a "concrete showing." Brief of Amicus Curiae United States at 23, *Festo II*, 535 U.S. 722 (2002) (00-1543).

[6] Proof by a fair preponderance of evidence is proof that shows something to be more likely true than not true. Clear and convincing evidence is "evidence that produces in the mind of the trier of fact an abiding conviction that the truth of the factual contentions are highly probable." Kevin Casey, et al., *Standards of Appellate Review in the Federal Circuit: Substance and Semantics*, 11 Fed. Cir. B.J. 279, 323 (2001) (internal quotations and citations omitted).

become as standardized as is the 'preponderance' formula"); *see also* Kevin Casey, et al., *Standards of Appellate Review in the Federal Circuit: Substance and Semantics*, 11 Fed. Cir. B.J. 279, 323 (2001) (noting that the clear and convincing standard is "not susceptible to precise definition").[7] Such a result is contrary to the purpose of prosecution history estoppel and, therefore, should be avoided.

Moreover, a burden of proof that is too exacting could result, *de facto*, in that which the Supreme Court in *Festo II* was trying to avoid—death of the doctrine of equivalents. *Cf.* Note, *Estopping the Madness at the PTO: Improving Patent Administration Through Prosecution History Estoppel*, 116 Harv. L. Rev. 2164, 2184 (2003) (noting that the Federal Circuit could make the burden of overcoming the presumption more stringent by requiring that patentees produce clear and convincing evidence). Proof by a fair preponderance of the evidence is less exacting than proof by clear and convincing evidence, thereby enabling the "presumption" outlined in *Festo II* to be one that practically can be rebutted—which in turn preserves the doctrine of equivalents. *See* Strong, *supra*, at § 340 (noting that the clear and convincing standard of proof is a "more exacting measure of persuasion" than preponderance of the evidence).[8]

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[7] Of course, there will always be a level of uncertainty in patent law that is inherently case-specific, but this uncertainty is exacerbated by the doctrine of equivalents and would be further exacerbated by an inconsistent application of the standard of proof necessary to rebut the "presumption." See John S. Golian, *Without A Net: The Supreme Court Attempts to Balance Patent Protection and Public Notice in Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 36 Creighton L. Rev. 541, 603 (2003) ("[T]he greatest amount of uncertainty is not created by the doctrine itself, but by the court's lack of a consistent application of the rule.").

[8] This burden of proof does not enable the doctrine of equivalents to be applied more broadly than has been its historic scope. *See Warner-Jenkinson*, 520 U.S. at 29 ("[T]he doctrine of equivalents when applied broadly, conflicts with the definitional and public-notice functions of the

Furthermore, the fair preponderance of the evidence standard generally is the one that is applied in patent law. David W. Okey, *Issued Patents and the Standard of Proof: Evidence Clear and Convincing or Merely Ponderous?*, 17 J. Marshall J. Computer & Info. L. 557, 587 (1999). In civil litigation, the clear and convincing standard is saved for special situations in which "a particular type of claim should be disfavored on policy grounds." Strong, *supra*, at § 340. Accordingly, in patent law, it is applied to challenges regarding validity because of the statutory provision found at 35 U.S.C. § 282, that a patent is "presumed" valid. Casey, *supra*, at 324. It is also applied when a patentee claims willful infringement of a patent, *Pall Corp.* v. *Micron Separations, Inc.*, 66 F.3d 1211 (1st Cir. 1995), or violation of the duty of disclosure. Casey, *supra*, at 324. While there are indeed public policy issues implicated in the doctrine of prosecution history estoppel, the "presumption" itself vindicates the public notice function of patent law. Thus, as already noted, to apply an overly exacting standard to a patentee's ability to overcome the "presumption" would unravel the balance the Supreme Court sought between protecting the true scope of a patent and honoring a competitor's reliance on the public record.

Based on this reasoning, the Court holds that the burden of proof most appropriate for overcoming the "presumption" of prosecution history estoppel is proof by a fair preponderance of the evidence.[9]

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statutory claiming requirement."). It ensures that prosecution history estoppel remains tied to its primary purpose without creating either more uncertainty or a complete bar that could eviscerate the doctrine altogether.

[9] During the July 28, 2003, motion hearing, the Court told the litigants that it was inclined to apply this burden of proof and both litigants agreed. 7/28/03 Mot. Hr'g Tr. at 58, ll. 5-8 and 59, ll. 14-21.

b. *The Federal Circuit's Analysis:* DID NOT ADDRESS THIS ISSUE.

Neither the Federal Circuit nor the Supreme Court has discussed the quantum of evidence required to rebut the presumption.

3. What Is The Role Of The Judge And The Jury?

a. *The Court's Original Analysis:* Anomalous as it may seem, the jury plays no role in any of this.

Although it is clear that the equitable doctrine of prosecution history estoppel is for the court to decide, *see, e.g.*, *Pioneer Magnetics, Inc.* v. *Micro Linear Corp.*, 330 F.3d 1352, 1356 (Fed. Cir. 2003); *CAE Screenplates Inc.* v. *Heinrich Fiedler GmbH & Co. KG*, 224 F.3d 1308, 1319 (Fed. Cir. 2000), the Supreme Court in *Festo II* did not provide guidance as to whether the determination that the patentee has rebutted the "presumption" is a question for the court or the jury. Though the bench trial in this case moots the issue here, the question generally remains.

Placing these fact questions before the jury could indeed work against the goals of consistency and predictability since the Federal Circuit would be required to defer to findings of fact made at the trial court level. *See* Raymond G. Areaux and Theodore S. Owers, III, Festo*'s Doctrine of Equivalents: Vitality Reaffirmed in View of New and Old Hurdles*, 48 Loy. L. Rev. 551, 576-78 (2002). On the other hand, determining whether the presumption has been rebutted is not purely technical in nature and involves the kinds of issues—foreseeability, intent, purpose, and reasonableness—normally reserved for a jury. *Cf.* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 Colum. L. Rev. 1035, 1096-97 (2003) (noting that "juries often decide questions of reasonableness even when facts are not in serious dispute."). Thus, unlike the circumstances in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370, 388-

90 (1996), where the Court concluded, with respect to claim construction, that "history and precedent provide no clear answers," here history and precedent do provide answers. These are matters historically resolved by American juries.

For the reasons already expressed in *Control Resources*, however, this Court predicts that litigation over the existence of prosecution history estoppel will be taken from the jury. *But see* Arthur R. Miller, *The Pretrial Rush to Judgment: Are the "Litigation Explosion," "Liability Crisis," and Efficiency Cliches Eroding Our Day in Court and Jury Trial Commitments?*, 78 N.Y.U. L. Rev. 982, 1087 (2003) (criticizing the decision in *Markman* v. *Westview Instruments, Inc.*, 517 U.S. 370 (1996), which embodies this trend in patent law). For the larger implications of marginalizing the jury's historic role, see William G. Young, An Open Letter to United State District Judges, Fed. Lawyer (2003). *See generally* Ellen E. Sward, The Decline of the Civil Jury (2003).

b. *The Federal Circuit's Analysis:* CONFIRMS THIS COURT'S PREDICTION BUT WITH A STRIKINGLY DIFFERENT ANALYSIS.

While the Federal Circuit characterizes the rebuttal question as it relates to the foreseeability criterion as involving mixed fact-law issues, *Festo III*, 2003 WL 22220526, at *5, it treats the issue as one for the district court (not a jury) to decide in the first instance. *Id.* at *4. This can be interpreted to mean that determining whether the "presumption" has been rebutted should be decided by the court because it arises in the context of an equitable defense and involves nuanced questions of mixed fact and law. This is the reading of *Festo III* that makes the most sense. It is fully supported by the cases cited by the Federal Circuit in this portion of the *Festo III* decision. *Id.* at *4 (citing *Loctite Corp.* v. *Ultraseal Ltd.*, 781 F.2d 861, 871 n.7 (Fed. Cir. 1985), *overruled on other grounds by Nobelpharma AB* v. *Implant Innovations, Inc.*, 141 F.3d 1059, 1068 (Fed. Cir. 1998); *Black & Decker, Inc.*

v. *Hoover Serv. Ctr.*, 886 F.2d 1285, 1295 (Fed. Cir. 1989); *Builders Concrete, Inc.* v. *Bremerton Concrete Prods. Co.*, 757 F.2d 255, 258 (Fed. Cir. 1985)). In other words, as the entire concept of prosecution history estoppel is a judicially created equitable doctrine, it makes prefect sense for the district court to do equity in the premises and make the necessarily nuanced fact finding subject to deferential appellate review.

The analysis above comports with prior Federal Circuit decisions and, moreover, is logical and practical.[10] Unfor-

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[10] This approach ensures that *Festo* issues need be addressed only in that small minority of patent cases in which they make a genuine difference. Since under *Dairy Queen, Inc.* v. *Wood*, 369 U.S. 469 (1962), jury issues must constitutionally be first resolved, the normal patent case to be tried to a jury ought proceed roughly as follows: Once the case is sufficiently mature, the court will hold a *Markman* hearing and construe the claims. This done, the court will normally consider a motion for summary judgment. *See, e.g., EMI Group N. Am., Inc.* v. *Intel Corp.*, 157 F.3d 887, 889 (Fed. Cir. 1998).

There are four possible outcomes:

1) The court rules there is no infringement, either literally or under the doctrine of equivalents. The *Festo* issue is gone.

2) The court rules that there is literal infringement. Normally, any lurking *Festo* issue now drops out of the case.

3) The court rules that there is no literal infringement but infringement may exist under the doctrine of equivalents. In this one circumstance, judicial economy may counsel proceeding directly to a *Festo* hearing before the court. If the outcome vitiates the claim under the doctrine of equivalents, the case is over. If, however, upon hearing, the "presumption" appears to have been rebutted, the jury trial will follow and the matter need finally be determined by the court only if the jury finds liability based upon the doctrine of equivalents. If the case is jury-waived, however, the court should decide the matter before determining whether there is infringement under the doctrine of equivalents.

4) There remain genuine issues of material fact concerning literal infringement. In this instance, the best course is to defer any consideration of *Festo* issues until after the jury trial. Not only does the Constitution

tunately, it appears not to be what the Federal Circuit intends—"[T]he determinations concerning whether the presumption of surrender has arisen and whether it has been rebutted are questions *of law* for the court, not a jury, to decide." *Festo III*, 2003 WL 22220526, at *4 (emphasis added). One could hope that the Federal Circuit meant only that the factual issues were reserved for the court given their equitable antecedents and that the phrase "of law" crept in during drafting without much thought. Such comforting yearnings are dashed, however, by the incisive dissent of Judge Newman who points out:

> This court now denies Festo the opportunity to present evidence as to the two criteria of tangentialness and some other reason, establishing these criteria as questions of law, not fact, and decides these questions of first impression without development and without evidence.

Id. at *18 (Newman, J., concurring in part and dissenting in part). In the face of this language, it would strain credulity to conclude that the majority intended something other than pure rulings of law, reviewed de novo on appeal.[11]

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command it, *Dairy Queen*, 369 U.S. at 471-72, it works smoothly. That is, in these circumstances knotty *Festo* issues need never be addressed unless the jury finds liability under the doctrine of equivalents—today, a finding unlikely to be upheld given the stringency with which the Federal Circuit applies this doctrine. *See e.g., Read Corp.* v. *Powerscreen of Am., Inc.* 44 Fed. Appx. 502, 505-10 (Fed. Cir. 2002) (unpublished).

[11] As the intensely fact specific discussion in the text here makes clear, however, this is an unworkable model. Despite the well grounded criticism of *Markman* (see section II.B.3.a), at least claim construction bears a rough analogy to statutory interpretation. Not so here. If these aspects of prosecution history estoppel are transmuted by fiat into pure matter of law reviewable de novo on appeal, every case with an amendment during the prosecution history will require its *Festo* hearing, even more lengthy and involved than the *Markman* hearings of today. This simply will not do.

4. Did The Supreme Court Define One Over-Arching Standard Or Three Distinct Criteria For Rebutting The Presumption?

   a. *The Court's Original Analysis: Festo II* provides one broad, over-arching standard for rebutting the "presumption" of prosecution history estoppel.

While Amgen and TKT/HMR agree that Amgen bears the burden of showing that the "presumption" of prosecution history estoppel is rebutted by a fair preponderance of the evidence, they disagree about what the evidence must show; that is, they interpret the Supreme Court's decision in *Festo II* differently. TKT/HMR asserts that *Festo II* depicts a single rebuttal standard: whether "at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." TKT/HMR's Mem. in Support at 2

Sadly, this is precisely the result predicted in the months before the *Festo III* decision issued:

> Now [I] suppose the [*Festo III*] opinion can come down and say these are all legal, these are all just legal questions. If they do . . . it reminds me of the story of Lincoln, great trial lawyer, he's arguing before a jury and . . . he looks over at the other lawyer and says 'how many legs does a sheep have?' The fellow says it has four. He says, 'now if I call a tail a leg, how many will it have?' And the fellow says it will have five. Lincoln turns to the jury and says 'no it won't, it still will have four. Calling the tail a leg doesn't make it a leg.' [Joseph F. Anderson, Jr., The Lost Art: An Advocate's Guide to Effective Closing Argument 120 (2002) (citing Victoria L. Eslinger's closing argument reciting this incident)].
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> . . . .
>
> I leave you with what's happening. Because of the complexity, because of the hostility to juries, what in fact you're doing is marginalizing yourselves, diminishing the District Courts, and the law is pretty much in the Federal Circuit.

Remarks of William G. Young, "Festo: Views from the Bench One Year Later" at BIO 2003, July 10, 2003.

(quoting *Festo II*, 535 U.S. at 741.) Amgen, on the other hand, argues that *Festo II* outlines three independent methods (described below) in which to rebut the "presumption" of estoppel. Amgen's Mem. in Opp'n re: '080 [Document No. 716] at 3, 7.

Upon reflection it appears that both parties are partly correct. Amgen is correct in asserting that *Festo II* lays out more than one way in which to rebut the "presumption" of estoppel. *See, e.g.*, *Schwing GmbH* v. *Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1329 (Fed. Cir. 2002) (citing various methods in which to rebut and remanding to the district court); *SoundTube Entertainment, Inc.* v. *Brown Innovations, Inc.*, 233 F. Supp. 2d 188, 196-97 (D. Mass. 2002) (Saris, J.) (applying the various methods of rebutting the presumption); *see also Amgen II*, 314 F.3d at 1345 (referring to *Festo II*'s "narrow ways" of rebuttal and citing the page in *Festo II* that sets out rebutting circumstances) (emphasis added). Indeed, in *Festo II*, the Supreme Court described three situations in which an amendment cannot reasonably be viewed as surrendering the equivalent in question: (1) when the equivalent was unforeseeable; (2) when the rationale underlying the amendment bears no more than a tangential relation to the equivalent in question; or (3) when some other reason exists that suggests that the patentee could not reasonably be expected to have described the insubstantial substitute in question.[12] *Festo II*, 535 U.S. at 740-41.

TKT/HMR, however, is also correct in asserting that the Supreme Court in *Festo II* made clear that to rebut the "presumption" of prosecution history estoppel, a patentee must "show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a

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[12] Amgen argues that TKT/HMR's purported standard is a paraphrase of this third situation. Amgen's Mem. in Opp'n at 3.

claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741. Upon careful review, it seems that this latter standard is a broad, over-arching one that embraces the three situations described above. When any of the three situations exist, the broad, over-arching standard necessarily is met. In other words, if the equivalent was unforeseeable, it would not have been *reasonable* to *expect* the patentee to have drafted the claim otherwise. Likewise, if the reason for the amendment was only tangentially related to the equivalent, it would not have been *reasonable* to *expect* the patentee to have drafted the claim so that it literally included the equivalent in question; that is, while the patentee perhaps *could have* drafted the claim otherwise to include the equivalent, it would not be *reasonable* to have *expected* it to have done so if the amendment was not even remotely related to the equivalent in question.[13] Finally, the third example simply illustrates that the Supreme Court recognized that the first two rebuttal methods were not exhaustive, that is, that there may yet be another reason why it would be unrea-

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[13] As will be discussed *infra*, it is important to note that the Supreme Court incorporated reasonableness and expectations into the standard. If the question was merely whether the patentee *could* have drafted a claim to encompass the equivalent then the test would simply be a foreseeability test. While some scholars have interpreted the Supreme Court's ruling to collapse the scenarios into one test about foreseeability, *see, e.g.*, Caliendo, *supra*, at 321, this Court declines so to read *Festo II*. If the standard were that simple, the Supreme Court would not specifically have called out the tangential example. Moreover, it would not have injected the notoriously equivocal concepts of "reasonableness" and "expectations" into what could have otherwise been a straightforward standard. *See, e.g.*, C. Alan Fu, *Prosecution History Estopel:* Festo Corp. v. Shoektsu Kinzoku Kogyo Kabushiki Co., 18 Berkeley Tech. L.J. 117, 137 (2003) (noting that the reasonableness test "softens the harsh standard that may be inherent in the foreseeability test" and that it is an "equitable idea").

sonable to expect the patentee to have drafted the claim to have encompassed the alleged equivalent.[14]

This interpretation is also supported by the language of the opinion itself. The Supreme Court, in describing the third rebuttal standard, used the words "some *other* reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question," *Festo II*, 535 U.S. at 741 (emphasis added). In using the words "some other reason," the Supreme Court indicated that the first two methods are merely specific ways to rebut the same broad presumption. Thus, the proper interpretation of the Supreme Court's language is that the first two methods are included within the broad, over-arching standard and the third is that Court's way of recognizing that other circumstances may also suffice to rebut the *Festo II* "presumption." This reading finds further support in the concluding sentence of this section of the opinion, wherein the Supreme Court summarizes the standard: "[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Id.* The fact that the Supreme Court summarized its analysis in this way suggests that one broad standard encompasses the three situations previously outlined.

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[14] Alternatively, *Festo II* might be interpreted to describe three distinct circumstances under which the "presumption" is rebutted: two specific and one more general. This interpretation is supported by the Federal Circuit's remand to the Court, in *Amgen II*, to interpret if any of the "narrow ways" of rebutting the "presumption" had been met. The Court, however, based on its interpretation of *Festo II* and the subsequent case law, views the three situations not as distinct, but as linked under a single, broad, overarching standard. Yet even if the Court did adopt the alternative interpretation, it would not substantively change this Court's analysis.

Most of the cases that have applied the holdings of *Festo II* also support this interpretation.[15] In *Bosch* v. *Japan Storage Battery Co., Ltd.*, 223 F. Supp. 2d 1159, 1170 (C.D. Cal. 2002), the court listed the three examples that the Supreme Court provided in *Festo II* and then summarized them by stating "[i]n short, '[t]he patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.'"[16] In *Varden Golf Co., Inc.* v. *Karsten Mfg. Corp.*, the court explained that the Supreme Court put the burden of showing that an amendment

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[15] Many of the scholarly articles written since the Supreme Court issued the *Festo II* decision also support this interpretation. *See, e.g.*, Daniel H. Shulman & Donald W. Rupert, *"Vitiating" the Doctrine of Equivalents: A New Patent Law Doctrine*, 12 Fed. Cir. B.J. 457, 462 (2003) ("The Supreme Court held that prosecution history estoppel would apply to additional subject matter not expressly relinquished if the patentee could have drafted a claim to cover the additional subject matter, but did not. The Supreme Court identified a number of reasons why a patentee might not have been able to draft such a claim."); John S. Golian, *supra*, at 543 ("The Court held that in order to rebut this presumption, a patentee must show that the amendment did not surrender a particular equivalent by demonstrating that 'one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.'"); *Leading Cases*, 116 Harv. L. Rev. 402, 407, 410 n.73 (2002) [hereinafter "*Leading Cases*"] (stating that the "the patentee may rebut the presumption by demonstrating that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent," outlining the two specific examples and noting that the Supreme Court "plainly did not intend these examples to be exclusive, adding that 'some other reason' may suffice to rebut the presumption of estoppel") (internal citations and quotations omitted).

[16] It should be noted, however, that in its analysis of the case, the California district court considered first whether the amendment was tangential and next whether it met the over-arching standard. It then concluded, based on the facts, that the patentee had failed to demonstrate both. *Bosch*, 223 F. Supp. 2d at 1172.

has not surrendered a particular equivalent on the patentee and implicitly indicated that this burden was "show[ing] at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Varden Gulf*, 2002 WL 1424567, at *4 (N.D. Ill. 2002). Later, when describing specific cases in which this burden was met, it stated that the Supreme Court's foreseeability example met the broad over-arching standard: "If for example the equivalent was unforeseeable at the time of the application, then the patentee could not reasonably be expected to have described the insubstantial substitute in question." *Id.* at *4; *see also Soundtube*, 233 F. Supp. 2d at 197 (summarizing the patentee's argument as "[the patentee] could not have foreseen the SoundTube system during the prosecution of the patent *and thus* 'one skilled in the art could not reasonably have been expected to draft claim limitations to literally encompass' the SoundTube devices") (emphasis added); *Glaxo Wellcom Inc.*, v. *IMPAX Labs Inc.*, 220 F. Supp. 2d. 1089, 1093 (N.D. Cal. 2002) (summarizing the standard as a single broad, over-arching standard); *ConMed Corp.* v. *Ludlow Corp.*, 235 F. Supp. 2d 109, 122 (N.D.N.Y. 2002) (applying the broad, over-arching standard and concluding that the patentee failed to meet its burden); *SmithKline Beecham Corp.* v. *Excel Pharms, Inc.*, 214 F. Supp. 2d 581, 591 (E.D. Va. 2002) (stating that, to meet its burden, the patentee must satisfy the broad, over-arching standard); *but see Schwing GmbH* 305 F.3d at 1329 (stating that the Supreme Court "discussed several ways in which the patentee could overcome [the] presumption" and listing the three examples from *Festo II* without connecting them to a single, broad, over-arching standard).

Thus, this Court interprets *Festo II* as providing a single standard—albeit a difficult one to satisfy—to determine whether the "presumption" of estoppel has been overcome

and as offering three situations in which the articulated standard would be satisfied.

b. *The Federal Circuit's Analysis:* DIFFERS FROM THIS COURT'S ANALYSIS BUT DOES NOT CHANGE THIS COURT'S ULTIMATE HOLDING.

The Federal Circuit holds that there are three separate "criteria" which the patentee may meet to rebut the "presumption." *Festo III*, 2003 WL 22220526, at *2, *5-*6 ("Specifically, the Court enumerated the three ways in which the patentee may overcome the presumption."). As mentioned above, whether the standard is viewed as three separate criteria or as one over-arching standard, will not, in most cases, change the end-result because the three criteria work in tandem with what this Court viewed as the over-arching standard. In other words, if the equivalent was unforeseeable, or if the reason for the amendment was no more than tangentially related to the equivalent, it would not have been *reasonable* to *expect* the patentee to have drafted the claim to have literally encompassed the equivalent.

The Federal Circuit's interpretation nevertheless may make a significant difference in the outcome of cases because it states that the third—the "some other reason"—criterion is to be narrowly construed. *Id.* at *5. Aside from stating that "a patentee may not rely on the third rebuttal criterion if the alleged equivalent is in the prior art . . . ." and that the "shortcomings of language" may satisfy the criterion, the Federal Circuit left to another day further exposition of this third criterion. *Id.* at *6.

5. What Type Of Evidence May Be Used To Rebut The Presumption?

   a. *The Court's Original Analysis:* Extrinsic evidence may be considered if it does not contradict the intrinsic evidence.

Although the rebuttal standard is narrow, the inquiry and analysis to determine if it has been met is in some respects intricate and, therefore, requires resort to extrinsic evidence. The Supreme Court made clear in *Festo II* that a court must examine the subject matter surrendered by the amendment and the reasonable inferences that can be drawn from the amendment. *Festo II*, 535 U.S. at 737-38; *Schwing GmbH*, 305 F.3d at 1329; *Bosch*, 223 F. Supp. 2d at 1170. This examination is more than a peripheral one.

> There is no reason why a narrowing amendment should be deemed to relinquish equivalents unforeseeable at the time of the amendment and beyond a *fair interpretation of what was surrendered.* Nor is there any call to foreclose claims of equivalence for aspects of the invention that have only a peripheral relation *to the reason the amendment was submitted.*

Festo II, 535 U.S. at 738 (emphasis added). To determine what was fairly surrendered by the amendment, the Court needs to, in many instances, understand the rationale for the amendment. *Id.* Knowing simply that an amendment was made for reasons related to patentability is not enough. The Court needs to understand more specifically why the exact words or limitations were added or deleted and such an understanding is not always immediately evident in the prosecution history. Often patentees change certain aspects of claims in response to an objection. Other times, such as in the case before the Court, patentees voluntarily make changes even when there is neither a Patent Office objection nor rejection and when no prior art threatens the validity of the

invention. Given that the "remarks" that accompany the amendments are cursory at best, in the latter case it is even more difficult to discern the particular rationale for the amendment based on the prosecution history. *Amgen I*, 126 F. Supp. 2d at 135 ("This search for purpose is made more difficult where, as here, there is nothing in the file wrapper as of the date of the amendment indicating that the claims were objectionable to the Patent Office."). Moreover, the "state-of-the-art" at the time of the amendment (a key piece of information necessary to determine foreseeability) generally is not something addressed in the prosecution history—nor are the intricacies of the technology always clear. Therefore, there are instances in which reliance on the prosecution history alone would not inform the court in sufficient detail as to why certain additions and deletions to the claims were made.

Notwithstanding these concerns, TKT/HMR relies on *Pioneer Magnetics* to argue that only the public prosecution history record can be used to demonstrate the purpose of the amendment and that the Court should not consider any extrinsic evidence in determining whether the rationale for the amendment has no more than a tangential relation to the equivalent in question.

TKT/HMR's argument is unavailing here. First, *Pioneer Magnetics* is distinguishable from the instant case. In *Pioneer Magnetics*, when the Federal Circuit stated that only the public record could be used to determine the purpose for the amendment, the court was evaluating whether the amendment was made for patentability reasons (a determination made prior to the assessment of whether the "presumption" of prosecution history estoppel has been overcome). *Pioneer Magnetics*, 330 F.3d at 1356. Thus, this holding is inapposite to the analysis that occurs *after* the court has decided that the amendment was a narrowing one made for patentability reasons and that the "presumption" therefore applies.

Second, neither *Pioneer* nor *Festo II* foreclose the use of extrinsic evidence once the "presumption" of estoppel has been triggered and the patentee is trying to rebut it. *See, e.g.*, Areaux & Owers, *supra*, at 574 (noting that the Supreme Court did not offer any guidance as to whether intrinsic or extrinsic evidence can be used). Moreover, in explaining that the interpretation of the patent *begins*—but does not end—with the literal claims and the prosecution history, *Festo II* apparently gave the patentee leeway to rely on extrinsic evidence to prove that "one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741; *but see* Pavan K. Argarwal, *Patenting in Line with the Federal Circuit*, 12 Fed. Cir. B.J. 395, 413-14 (2003) ("[W]ith the notice function that the Supreme Court previously announced in *Warner-Jenkinson Co.* v. *Hilton Davis Chemical Co.*, it would seem appropriate to limit the patentee to the public record of the prosecution as the en banc Federal Circuit decided in *Festo*.").

Third, the United States Amicus Brief—relied on by the Supreme Court to define the rebuttable "presumption"—argued that extrinsic evidence can be used that explains but does not contradict intrinsic evidence. Brief of Amicus Curiae United States at 23, *Festo II*, 535 U.S. 722 (2002); Areaux & Owers, *supra*, at 575-6 (noting that the U.S. Amicus Brief was a clue to what type of evidence the Federal Circuit will allow). Moreover, it specifically urged that facts should be drawn from the specific technology involved. Brief of Amicus Curiae United States at 23 n.4. Even the Federal Circuit in *Festo I* (which stated that use of extrinsic evidence would undermine the public notice function) explained that a district court can properly consider any argument made by an attorney that is supported by the prosecution history record. *Festo I*, 243 F.3d at 586 n.6.

Lastly, common sense dictates that extrinsic evidence may be necessary to meet the rebuttal requirements outlined in

Festo II. For example, the prosecution history alone would not show whether an invention, discovery, or technique was foreseeable, or whether a person skilled in the art could have drafted the claim differently. *See, e.g.*, Areaux & Owens, *supra*, at 575 ("[I]t seems plain that evidence of foreseeability will not reside in the prosecution history."). Furthermore, it is the prosecution history itself that triggers the "presumption" of estoppel; thus, if the patentee is limited to the prosecution history in its efforts to rebut that "presumption," it would likely never be successful. Like a standard of proof that is too exacting, limiting the patentee to the intrinsic record would in essence create a result similar to the complete bar the Supreme Court overruled in *Festo II.*

For these reasons, in determining whether Amgen has rebutted the "presumption" of estoppel, the Court will examine the prosecution history in light of the presentations made during the trial and in the parties' submissions. *Cf. Canton Bio-Medical, Inc.* v. *Integrated Liner Tech., Inc.*, 19 F. Supp. 2d 22, 32 (N.D.N.Y. 1998) (relying in part on expert opinion to determine what was surrendered with the amendment and holding that "[a]fter considering the arguments of the parties, their briefing and submissions, the entire relevant record, and the applicable law, the [c]ourt finds that the Defendant's accused process does not infringe the Plaintiff's [] patent, as a matter of law, based on the application of prosecution history estoppel . . . .").[17]

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[17] This case along with other cases predating *Festo II* support the Court's reference to extrinsic evidence. At least one other federal court has relied on extrinsic evidence to aid the analysis. *See, e.g., Envirco Corp.* v. *Clestra Cleanroom Inc.*, 1998 WL 809369, at *3 (N.D.N.Y. Nov. 4, 1998) (noting that determining prosecution history estoppel is based on the patent, specification, and the prosecution history, but if the court requires extrinsic evidence to construe the claims, it may rely on dictionaries, treatises, and, if needed, expert opinion), *vacated on other grounds by Envirco Corp.* v. *Clestra Cleanroom Inc.*, 209 F.3d 1360 (Fed. Cir. 2000).

In other words, the Court will consider extrinsic evidence. It will do so, however, only when that evidence does not *contradict* the intrinsic evidence—the patent, the specification, and the prosecution history. Such an examination thus cannot dissuade the Court from giving the public record its due weight—a significant policy on which patent law is based. Moreover, the Court will not go so far as to consider the subjective intent of the patentees when such intent is not expressed in or supported by the patent or file wrapper. "Such testimony cannot guide the court to the proper interpretation when the patent documents themselves do so clearly." *Vitronics Corp.* v. *Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996). When, however, such intent is supported by the prosecution history, the Court will consider it because "a full understanding of what the inventors actually invented and intended to envelop with the claim" guides a court to the proper interpretation. *Renishaw PLC.* v. *Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (discussing claim construction). These limitations on the Court's consideration of extrinsic evidence strike the proper balance between supporting the notice functions of the patenting process and protecting the true scope of an inventor's patent despite the ineptness of language to do so on its own.[18]

b. *The Federal Circuit's Analysis:* RESTRICTS THIS COURT'S APPROACH

The Federal Circuit adopts a more restrictive approach to extrinsic evidence than that set out above. *Festo III*, 2003 WL 22220526, at *5-6. Both this Court and the Federal Circuit interpret *Festo II* as allowing consideration of extrinsic evidence when determining whether the first criterion, fore-

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[18] Although the Court holds that consideration of extrinsic evidence is necessary adequately to determine whether the rebuttal standard laid out in *Festo II* has been met, it recognizes that such consideration, along with other patent law analyses like *Markman*, blur the line between the role of judge and jury. *See* section II.C.3, *supra*.

seeability, has been met. *Id.* The Federal Circuit, however, clearly limits the determination under the second criterion, tangentiality, to intrinsic evidence and strongly suggests that the third criterion should be limited in the same way.[19] *Id.* This is the crucial difference between its analysis and that of this Court. Notwithstanding the revisions necessary to comport with the Federal Circuit's analysis, the Court's holding that Amgen has rebutted the presumption has not changed. The basis for this holding, however, rests on different criteria, as will be explained below.

6. Should Foreseeability Be Analyzed At The Time Of The Amendment Or The Time Of The Original Patent Application?[20]

a. *The Court's Original Analysis:* Foreseeability Should Be Analyzed At The Time Of The Amendment

Some scholars and courts have indicated that the Supreme Court was not clear whether foreseeability should be analyzed at the time of the amendment or at the time of the application. *See, e.g.*, Caliendo, *supra*, at 321; Fu, *supra*, at 134 (noting that the Supreme Court was unclear with respect to when the foreseeability test should be applied).

This Court, however, holds that *Festo II* defined the relevant time period as the time of the amendment, not the time

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[19] The Federal Circuit did not completely rule out resort to extrinsic evidence in determining the third criterion. It stated that intrinsic evidence should be used "when at all possible" and that it "need not decide now what evidence outside the prosecution history record, if any, should be considered in determining if a patentee has met its burden under this third rebuttal criterion." *Festo III*, 2003 WL 22220526, at *6. In *Festo III*, the issue was not squarely before the Court as it is here.

[20] The parties disagree about whether foreseeability, the first criterion, should be analyzed with respect to what was known by those skilled in the art at the time of the original patent *application* or at the time the narrowing *amendment* was made.

of the patent application. First, in *Festo II* the Supreme Court explicitly stated twice that the relevant time period is the time of the amendment. When it first explains why a narrowing amendment should not be deemed to relinquish all equivalents, it considers foreseeability based upon what was known at the time of the amendment. *Festo II*, 535 U.S. at 738. Later, when it summarizes the holding of *Festo II*, the Federal Circuit again states that the "presumption" may be rebutted when the patentee "show[s] that at the *time of the amendment* one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Id.* at 741 (emphasis added). Although the Supreme Court used the word "application" in describing the foreseeability test at one point, *see Festo II*, 535 U.S. at 740 ("The equivalent may have been unforeseeable at the time of the application . . . ."), the Court was referring to the application process, not the time at which the application was originally filed. *Cf. Johnson & Johnston Assoc. Inc.* v. *R.E. Serv. Co.*, 285 F.3d 1046, 1059 (Fed. Cir. 2002) (Rader, J., concurring) ("In reaching this result, the court suggested that if variation had been unforeseeable during the application process, the doctrine of equivalents would still have been available to the patentee.").

Second, the Federal Circuit and other federal courts have also interpreted the relevant time reference to be the time of the amendment (not the time of the application). *See, e.g.*, *Pioneer Magnetics*, 330 F.3d at 1357 (analyzing foreseeability based on what was known at the time of the amendment); *SmithKline*, 214 F. Supp. 2d at 592 (same); *Masco Corp.* v. *United States*, 56 Fed. Cl. 400, 412 n.11 (2003) (noting that there is some support for interpreting *Festo II* as requiring unforeseeability at the time of the amendment).

Third and finally, common sense dictates the same interpretation. Prosecution history estoppel only arises when an amendment has been made that potentially surrenders an

equivalent. *See* Fu, *supra*, at 134 (noting that the more logical time to apply the foreseeability test is at the time of the amendment). The key inquiry is what was known at the time the patentee added the words now being used to estop it from arguing the equivalent.

Amgen strenuously argues that the relevant time period is the time of the application because when amending a patent application, an applicant is limited to the written description and drawings that were in the application at the original filing date and cannot add new matter to an application, even to correct an error in the specification or claims. Amgen's Post-Hr'g Mem. [Document No. 742] at 5. This argument is unavailing because a patentee certainly can—instead of amending—file a continuation-in-part application if the original written description and drawings do not lend themselves to the desired amendment. *See* 35 U.S.C. § 120, 112.[21] In other words, if, as Amgen suggests, there is new matter to add that is necessary to complete or correct the patent description and protect the invention, the patentee can and should re-file the application instead of creating a make-shift amendment to patch up the patent's deficiencies.[22] Therefore, the Court

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[21] A continuation-in-part application generally is one that claims some subject matter common to the parent application but also adds new matter that is not common to and not supported by the parent application. *See e.g.*, *Reynolds Metals Co.* v. *Continental Group Inc.*, 525 F. Supp. 950, 970 (N.D. Ill. 1981); *Chisholm-Ryder Co.* v. *Lewis Mfg. Co.*, 398 F. Supp. 1287, 1289 (W.D. Pa. 1975); *Chemithon Corp.* v. *Procter & Gamble Co.*, 287 F. Supp. 291, 298 (D. Md. 1968). The original filing date, however, applies only to the subject matter that is common to both the parent application and the later-filed application: "[A]ny claims therein that include new matter are only entitled to the actual filing date of the later-filed application, and not the earlier parent application." *Reynolds*, 525 F. Supp. at 970; *Application of Van Langenhoven*, 458 F.2d 132, 136 (C.C.P.A. 1972) ("[S]ubject matter which is first disclosed in a continuation-in-part application is not entitled to the filing date of the parent application."); *Chisholm-Ryder*, 398 F. Supp. at 1289.

[22] Amgen's argument that this is new matter suggests that an amend-

interprets the Supreme Court's holding in *Festo II* as requiring foreseeability to be adjudged relevant to the time the *amendment* was made.

b. *The Federal Circuit's Analysis:* SUPPORTS THIS COURT'S CONCLUSION

Although the Federal Circuit did not explain its conclusion, the recent Federal Circuit opinion in *Festo III* makes clear that foreseeability should be analyzed at the time of the amendment. *Festo III*, 2003 WL 22220526, at *5 (stating repeatedly that this criterion asks "whether the alleged equivalent would have been unforeseeable to one of ordinary skill in the art *at the time of the amendment*") (emphasis added).

C. Has Amgen Rebutted The "Presumption" Of Estoppel?[23]

The following analysis is conducted in light of the Federal Circuit's recent decision in *Festo III*.

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ment was not the correct vehicle to make its desired changes but instead that the more appropriate action would have been for Amgen to have filed a continuation-in-part application. *Cf. Application of Hafner*, 410 F.2d 1403, 1406-07 (C.C.P.A. 1969) (noting that a fatal defect cannot be cured by an amendment). Of course, if it had done this, it would not have had the benefit of the filing date of the earlier application. *Id.*

[23] The Court proceeds directly to determining whether Amgen has rebutted the "presumption" of estoppel. Normally, a court would first analyze whether a *narrowing* amendment had been made for reasons related to patentability (thereby invoking the "presumption" of prosecution history estoppel) and then proceed to determine if the "presumption" was adequately rebutted. *Pioneer Magnetics*, 330 F.3d at 1356-57 (dividing the analysis into three parts: (1) whether the amendment was a narrowing one; (2) whether the amendment was made for reasons related to patentability; and (3) whether the presumption can be overcome); *Soundtube*, 233 F. Supp. 2d at 195-97 (separating the analysis into two parts: "Narrowing Amendment" and "Surrender"). Here, however, the Federal Circuit upheld the Court's determination that the amendment was a narrowing one made to overcome a double patenting objection. Further, the Federal Circuit held that this amendment was therefore related to patentability such that the presumption of prosecution history estoppel would apply. *Amgen II*, 314 F.3d at 1345.

Applying the rules laid out in *Festo II* as interpreted by the Federal Circuit in *Festo III*, the Court begins with the presumption that Amgen has surrendered all the equivalents that fall within the territory between the original claims of the application for the '080 patent and the subsequently narrowed claims of the '080 patent. *See Festo II*, 535 U.S. 733-34; *Festo III*, 2003 WL 22220526, at *4. When the application for the '080 patent was originally filed, it contained 60 claims. These claims did not limit the invention to human EPO nor did they limit the claims to the amino acid sequence of Figure 6. In the third preliminary amendment, Amgen added the following limitation: the "mature human erythropoietin sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App. [Document No. 708], Tab E at 7.

As explained in *Amgen I*, Figure 6 displays the nucleotide series or DNA sequence of human EPO including both exons (the portions of the sequence that code for the desired protein) and introns (the portions of the sequence that do not code for the protein and are spliced out during transcription). *Amgen I*, 126 F. Supp. 2d at 100. Figure 6 also shows a series of codons, sets of three adjacent nucleotides that determine which of the twenty amino acids are incorporated into a protein at a particular location. *Id.* Each amino acid is identified by its three letter abbreviation representing a codon. *Id.* Figure 6, therefore, demonstrates the deduced amino acid sequence that is arrived at by reading the codons of the DNA encoding the protein. *Id.* Figure 6 numbers the amino acids from -27 to a final position of 166, which is labeled arginine. Because the *original* claims covered all human EPO regardless of the number of amino acids, but the amended claims limited the EPO to Figure 6 (depicting a 166 amino acid sequence), Amgen is presumptively barred from claiming equivalent infringement by a human EPO product containing anything other than that depicted in Figure 6, such as HMR/TKT's EPO which comprises a 165 amino acid sequence.

Amgen attempts to overcome the "presumption" by arguing (1) that HMR 4396, that is, a mature human EPO with a 165 amino acid sequence, was not foreseeable at the time of the application; (2) that the rationale for the amendment bears "no more than a tangential relation to the equivalent in question," *Festo II*, 535 U.S. at 740; and (3) that there is another reason why Amgen could not reasonably be expected to have drafted a claim that encompassed the alleged equivalent.

TKT/HMR argues that Amgen cannot meet the requirements of *Festo II* to rebut the presumption of estoppel because (1) Amgen could have made its claim without specifying the amino acid sequence (Figure 6) in its entirety or at all; and (2) the claims of the original '080 patent covered all EPOs (including the TKT/HMR product) and by amending the claims to include a reference to Figure 6, Amgen surrendered this broad coverage. TKT/HMR's Mem. in Support re: '080 [Document No. 679] at 2.

Before addressing these arguments, a review of the prosecution history is necessary.

1. The Prosecution History Of The '080 Patent

In the first preliminary amendment, the original 60 claims were canceled and new claims 61-67 added. June 6, 1995 Amendment, TKT/HMR's App., Tab E. Of importance to this case are claims 61, 62, 63, and 64.

> 61. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having glycosylation which differs from that of human urinary erythropoietin.
>
> 62. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources having a higher molecular weight than human urinary erythropoietin as measured by SDS-PAGE.

63. An isolated human erythropoietin glycoprotein product not being isolated from human urinary sources and free of other human proteins.

64. The in vivo biologically active erythropoietin product of the process comprising the steps of:

(a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6, (2) the protein coding sequences set out in FIGS 5 and 6, and (3) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (1) and (2) or their complementary strands; and

(b) isolating said erythropoietin product therefrom.

Id.

Thereafter, in the Second Preliminary Amendment, Amgen canceled product claims 61-63, amended process claim 64 to specify that it was a non-naturally occurring in vivo biologically active EPO product, and added new "product-by-process" claim 68. *Id*; Amgen's Post-Hr'g Mem. in Support at 12, n.12; December 20, 1995, Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120.[24]

68. A non-naturally occurring erythropoietin product of the process comprising the steps of:

a) growing, under suitable nutrient conditions, host cells transformed or transfected with an isolated DNA sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof; and

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[24] It also changed the dependency of claim 65 from "according to claim 61, 62, 63 or 64" to "according to claim 64 or 68." Amgen's Post-Hr'g Mem. at 12; December 20, 1995, Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-20.

b) isolating an erythropoietin product therefrom.

Id.

Amgen then amended the claims again. In this third preliminary amendment, Amgen cancelled claims 64-68 and inserted new claims 69-75. Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E. Claims 69, 70, and 71 became claims 1, 2, and 3 of the '080 patent and are, therefore, the claims of interest here.

> 69. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and has glycosylation which differs from that of human urinary erythropoietin.
>
> Claim 70. An isolated erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6 and is not isolated from human urine.
>
> Claim 71. A non-naturally occurring erythropoietin glycoprotein having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of Figure 6.

Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 8.

2. Was The Equivalent Foreseeable?

As discussed *supra*, foreseeability is one of the bases on which to determine whether the standard for rebutting the "presumption" is met. If the equivalent in question was not

foreseeable at the time of the amendment, then the patentee can overcome the "presumption."

Unfortunately for Amgen, it supports its foreseeability argument primarily with expert testimony that addresses knowledge of those skilled in the art *at the time of the application*, as opposed to the time of the amendment (the relevant time period). *Festo II*, 535 U.S. at 741. Amgen claims (and TKT/HMR does not dispute) that it was unknown, at the time of the patent *application*, that the 166th amino acid cleaved off to leave a 165 amino acid sequence. Accordingly, Amgen argues, it was unforeseeable (at the time of the application) that Figure 6's depiction of a sequence of 166 amino acids did not cover all mature human EPOs (including TKT/HMR's HMR 4396). Moreover, it argues that it was unforeseeable that the mature human EPO glycoprotein produced in Example 10 would contain only the 1-165 amino acid sequence.

Crucially, Amgen made admissions in its submissions and oral argument that it—as well as those skilled in the art—knew at the time of the amendment that human urinary EPO had a 165 amino acid sequence. Amgen's Mem. in Support at 10; 7/28/03 Mot. Hr'g Tr. at 71, ll. 11-20; 7/31/03 Mot. Hr'g Tr. at 77, ll. 12-18.[25] In fact, on October 30, 1987, Amgen explained in its FDA product license application that the 166th arginine (depicted in Figure 6) cleaves off leaving 165 amino acids (instead of the originally believed 166):

> The Arg 166, coded for by the erythropoietin gene (Section 2.B) appears to be cleaved post-translationally, resulting in a C-terminus residue of Asp 165. The detailed analysis of the C-terminus of erythropoietin is described later in this Section.

Trial Ex. 2024 at AM 57 007747. Therefore, Amgen cannot meet its burden here. Amgen's argument that this admission

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[25] As discussed, *supra*, consideration of extrinsic evidence is entirely proper under this criterion. *Festo III*, 2003 WL 22220526, at *5-6.

does not show that it was foreseeable that the *amendment (that incorporated the Figure 6 limitation) would be construed* by this Court to exclude human EPO with a 165 amino acid sequence is unavailing at this juncture in the analysis.[26] Simply because the Court's construction (that resulted in a complete surrender of an equivalent human EPO with a 165 amino acid sequence) was not foreseeable at the time of the amendment does not mean that the equivalent was not itself foreseeable—which is the correct inquiry. *See Masco*, 56 Fed. Cl. at 413 (finding unavailing patentee's argument that surrender was not foreseeable because it did not have the Court's claim construction); *SmithKline*, 214 F. Supp. 2d at 592 n.23 ("[T]he issue before this court is whether the patentee had the scientific ability to redraft the claims more broadly . . . .").[27] Although this places a "premium on

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[26] In *Amgen I*, Amgen argued that the amendment should be construed to mean "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Amgen I*, 126 F. Supp. 2d at 86. TKT/HMR contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6." *Id.* The Court agreed that the term "mature" meant the fully processed form of EPO secreted by the cell, *id.*, but found that the Figure 6 limitation constricted the meaning of the claim terms to the entire 166 amino acid sequence disclosed in the figure. *Id.* at 100. As will be discussed in greater length, *infra*, Amgen has now submitted extrinsic evidence indicating that Amgen intended the amendment to cover human EPO with a 165 amino acid sequence and that the Patent Office and those skilled in the art interpreted the amendment to do just that. While this evidence is important to the Court's analysis under the third criterion, it is not relevant with respect to whether the equivalent itself was foreseeable.

[27] This is not to say that Amgen's inability to predict the Court's claim construction is wholly irrelevant to whether Amgen can rebut the "presumption." On the contrary, as will be discussed below, there is a reasonableness element to the third criterion of *Festo II*. The fact that Amgen and one skilled in the art would have construed the amendment to cover human EPO with a 165 amino acid sequence may suggest that it is not reasonable to expect Amgen to have drafted the claim otherwise. That being said, this argument is not relevant with respect to whether the

forethought of patent drafting," this premium is not new to the doctrine. *Sage Prods., Inc.* v. *Devon Indus., Inc.*, 126 F. 3d 1420, 1425 (Fed. Cir. 1997); *Johnson & Johnston*, 285 F.3d at 1057 (Rader, J., concurring) ("A foreseeability bar thus places a premium on claim drafting and enhances the notice function of claims. To restate, if one of ordinary skill in the relevant art would reasonably anticipate ways to evade the literal claim language, the patent applicant has an obligation to cast its claims to provide notice of that coverage. In other words, the patentee has an obligation to draft claims that capture all reasonably foreseeable ways to practice the invention."). Here, given its knowledge of human EPO having 165 amino acids, Amgen had "every incentive to redraft the claims as broadly as possible in an effort [to] surrender no more subject matter than necessary to secure the patent." *SmithKline*, 214 F. Supp. 2d at 592. For example, Amgen might have deleted the reference to Figure 6 altogether and claimed "mature human EPO" instead of limiting it to a sequence.[28] Indeed, Amgen admits that it

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equivalent was foreseeable, and, therefore, Amgen cannot rebut the "presumption" based on foreseeability.

[28] TKT/HMR also asserts that Amgen could have drafted a claim that covered human EPO with a 165 amino acid sequence by claiming a fragment or portion of Figure 6 as it did in other claims. TKT/HMR's Mem. in Support at 7. In claim 4 of the '933 patent, "the human erythropoietin amino acid sequence set out in FIG. 6 or a fragment thereof" was claimed. Similarly, the original claim 26 of the 1984 application for the '080 patent sought coverage of "part or all of" the 166 amino acid sequence in Figure 6:

> 26. A synthetic polypeptide having *part or all* of the amino acid sequence set forth in Table VI, other than the residues within the sequence numbered 1 through 20, and having the immunological properties of naturally-occurring human erythropoietin.

Trial Ex. 2411, TKT/HMR's App., Tab C at 64 (emphasis added).

Amgen makes various counter-arguments as to why amendments with these exact words were not possible with respect to the product claims at

"could have sought broader claims that literally encompassed human EPO with a 165 amino acid sequence, and did in fact do so in the '422 patent [U.S. Patent No. 5,955,422]."[29] Therefore, Amgen cannot prevail under this prong of the analysis. The determinative factor here is that the alleged equivalent was foreseeable. In fact, it was known and could easily have been encompassed in the amendment. Thus, Amgen has not met its burden with respect to the foreseeability criterion.

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issue. The Court declines to consider issues that are not determinative here. Amgen does not dispute that it could have claimed "mature human EPO" instead of delineating a sequence. Simply put, if it had merely stated "mature human EPO" instead of specifying Figure 6, arguably it would have served Amgen's purported purpose of distinguishing '080 as "only human" (and not "human and nonhuman") *and* it would have encompassed the alleged equivalent. Any argument that these words would not have been successful in avoiding a double-patenting objection is irrelevant to whether the equivalent was foreseeable and within the patentee's ability to be included in the amendment. *See SmithKline*, 214 F. Supp. 2d at 592 n.23 (noting that "whether the examiner would have accepted the hypothetical amendments" was not relevant to whether the patentee had the scientific ability to draft the claims to encompass the alleged equivalent).

[29] Amgen argues that the relevant inquiry is whether Amgen could have claimed the 1-165 amino acid sequence of Figure 6 specifically—not whether Amgen could have drafted a claim that would have encompassed it. Amgen's Post-Hr'g Mem. at 8-9. The Court disagrees. While it is true that the Supreme Court stated that a patentee could overcome the "presumption" by showing "some other reason suggesting that the patentee could not reasonably be expected to have *described* the insubstantial substitute in question," this must be read in the context of the entire opinion. Elsewhere the Supreme Court used the word "embrace" and "encompass." *Festo II*, 535 U.S. at 734, 741. This is not a judgment about the strength of Amgen's arguments that it could not specifically call out a 165 amino acid sequence because it is new matter. Instead, the Court views these arguments as irrelevant to the analysis because Amgen simply could have employed the more general description noted above, that is, "mature human EPO" or "human erythropoietin."

3. Was The Rationale Underlying The Amendment No More Than Tangentially Related To The Equivalent?

Although the Court has determined that the 1-165 amino acid human EPO equivalent was indeed foreseeable, Amgen can rebut the "presumption" of prosecution history estoppel if it can show by a preponderance of the evidence that the rationale underlying the amendment was only tangentially related to the equivalent. *Festo II*, 535 U.S. at 740.[30] With respect to this standard, more than the others, the *purpose* of the amendment comes to the forefront of the analysis. Contrary to some scholars' views, the correct inquiry is not whether the amendment itself narrows the scope of a claim in

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[30] Neither the Supreme Court, nor the Federal Circuit has yet provided explicit guidance as to what qualifies as a tangential relationship. The few district court cases and the Federal Circuit's *Festo III* decision that address the issue are not particularly helpful here. For example, in *Soundtube* it was clear that the purpose of the amendment was directly related to the equivalent in question because the patentee had "trumpeted the benefits of a constant radius" in its design and "argued that this feature distinguished his invention from the prior art and satisfied section 112 concerns." *Soundtube*, 233 F. Supp. 2d at 198. In *Bosch*, the prosecution history itself showed that the purpose of the amendment was related to the equivalent in question. *Bosch*, 223 F. Supp. 2d at 1172. There, the patentee had argued that the purpose of the amendment was to narrow the location of a certain aspect of the invention, not its shape. *Id.* The Patent Office, however, rejected a final version of the claim that specified the location but not the shape. *Id.* In *Festo III*, one of the amendments was made in response to a rejection and both of the amendments were made to distinguish prior art patents based, partially, on an aspect of the invention relating to the equivalent. *Festo III*, 2003 WL 22220526, at *8- 9. Here, the intrinsic evidence is not so plain. No prior art disclosed any sequence of human EPO let alone one with a 1-165 amino acid sequence. Therefore, no claim can be made that Amgen was trying to distinguish its claims over such equivalent. Moreover, there was no rejection indicating that it was the depiction of 166 amino acids, as opposed communicating "human," that made the difference in patentability.

a way that affects the equivalent in question.[31] If this were the test, it would be an impassable one—the only reason why the dispute arises is *because* the equivalent is related to the amendment and thereby affected. The correct inquiry is whether the *rationale* underlying the amendment, the "reason the amendment was submitted"—not the amendment itself—is more than peripherally related to the equivalent in question. *Festo II*, 535 U.S. at 738, 740 ("Nor is there any call to foreclose claims of equivalence for aspects of the invention that have only a peripheral relation to *the reason the amendment was submitted*. . . .[T]he rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question . . . .") (emphasis added). Thus, the Court must delve deeper to determine whether the rationale underlying the amendment to the '080 patent was tangential to the equivalent in question. While it is undisputed that the amendment was made to avoid a double patenting objection,[32] the parties disagree about why the amendment was so constructed, that is, why Amgen used the exact language it did to distinguish the '080 patent from Amgen's '933 patent. Moreover, in light of the Federal Circuit's mandate that the Court rely only on intrinsic evidence in this criterion, determining the purpose of the amendment is made even more "thorny" because the amendment was not made to address a rejection or objection actually made or described by the Patent Office. *Amgen I*, 126 F. Supp. 2d at 135.

Amgen argues primarily that it amended its claim to specify that the '080 patent referred to the mature *human*

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[31] C. Alan Fu, in his article in the Berkeley Technology Law Journal, noted that the Supreme Court did not specify what the tangential relationship was but that this was the most logical reading of the test. Fu, *supra*, at 136.

[32] To be clear, the '080 claims were never rejected for double patenting; rather, the amendments were made voluntarily and preemptively to distinguish the '080 claims from claim 1 of Amgen's '933 patent. Amgen's Post-Hr'g Mem. at 10; *Amgen I*, 126 F. Supp. 2d at 135.

EPO (which can be described as having the amino acid sequence of Figure 6) and not to distinguish or exclude a 165 amino acid human EPO such as TKT/HMR's HMR 4396. Amgen's Mem. in Opp' n at 12.

The prosecution history supports Amgen's contention. Amgen's '933 patent issued just before this amendment was made. It claimed human and non-human EPO. When the application for the '080 patent was filed, it contained 60 claims, none of which limited the EPO protein products to "human" EPO. Amgen's Post-Hr'g Mem. at 11. As described in detail above, in a preliminary amendment, those original 60 claims were canceled and new claims 61-67 were added. June 6, 1995 Preliminary Amendment, TKT/HMR's App., Tab E. Claims 61-63, product claims, were indeed limited to a human EPO glycoprotein product. *Id.* In a second preliminary amendment, however, all but two claims (which were amended) were cancelled, and a new "product-by-process" claim was added. Amgen's Post-Hr'g Mem. at 12; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120. At this point, there is no dispute that the claims, as depicted in the second preliminary amendment were not limited to "human" EPO.[33] In a third preliminary amendment

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[33] Interestingly, two of these claims did indeed mention Figure 6 and one mentioned "human." Process claim 64 limited the technique to "host cells transformed or transfected with an isolated DNA sequence selected from the group consisting of (1) the DNA sequences set out in FIGS 5 and 6." TKT/HMR's Appendix, Tab E. Process claim 68 recited a technique that involved growing host cells "transformed or transfected with an isolated DNA *sequence encoding the human erythropoietin amino acid sequence set out in FIG. 6* or a fragment thereof." (emphasis added). Amgen's Post-Hr'g Mem. at 12; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 119-120. TKT/HMR does not assert that these two claims limit the claim to *human EPO* and Amgen argues that it does not so limit it. This may be because these are process, not product, claims. Regardless, because it is undisputed, the Court does not read the emphasized phrases so to limit the claims.

(the amendment at issue in this case), Amgen changed the product-by-process claims back to product claims adding the limitation at issue here: "the mature erythropoietin amino acid sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E (canceling claims 64-68 and adding new claims 69-75).

TKT/HMR's main counter-argument is that Amgen had previously referred to an "isolated *human* erythropoietin glycoprotein" and, therefore, could not have been amending in order to distinguish this claim on the basis of human EPO versus non-human EPO. TKT/HMR's Mem., Tab E (emphasis added). TKT/HMR, however, compares the third (and final) preliminary amendment with the first preliminary amendment, failing to account for the fact that the second preliminary amendment did not so limit the claims to human EPO. Neither Amgen nor TKT/HMR provide any evidence as to why Amgen changed the claims from product claims to product-by-process claims and then back again, nor do they provide evidence as to why the claims were (in the first amendment) limited to human EPO and then not so limited (in the second amendment) and then finally limited again (in the third amendment). *See, e.g.*, 7/31/2003 Mot. Hr'g Tr. at 76, ll. 1-25 (describing the chronology of amendments and stating that Amgen does not know why the limitation to "human" was dropped out when the claim was put into a product-by-process claim). Regardless of the reason why Amgen switched back and forth, the chronology and language of the amendments support Amgen's position that it added the amendment in question (the third amendment) to distinguish the '080 patent from the '933 patent on the basis that '080 was limited to *human* EPO.[34]

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[34] Both parties agree that a patentee can patent a product for human *and* non-human EPO and also patent a product for only human EPO. This does not run awry of the double-patenting rule because the same invention is not claimed in both patents. An EPO product could literally infringe the

This position is also supported by Amgen's statements to the Patent Office. In its remarks accompanying the third preliminary amendment, Amgen told the Patent Office that it distinguished the '080 patent from the '933 patent by "specifying that the claimed subject matter [of the '080 claims] comprises the mature *human* erythropoietin sequence of Figure 6." Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 9 (emphasis added).[35]

In further support of Amgen's argument that it did not amend to distinguish the '080 patent from human urinary EPO that has a 165 amino acid sequence, it points to the fact that it told the Patent Office that glycosylation and source limitations—not the Figure 6 limitation—distinguished the EPO of its amended '080 claims from human urinary EPO. *Id.*[36] This indicated to the Patent Office that Amgen was not

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claims of one patent without literally infringing the claims of the other. For example, monkey EPO could literally infringe the patent that claims both human and non-human EPO, but it would not literally infringe the patent that claims only human EPO. *See In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970) (noting that 35 U.S.C. § 101 "prevents two patents from issuing on the same invention. . . . By 'same invention,' we mean identical subject matter. Thus, the invention defined by a claim reciting 'halogen' is not the same as that defined by a claim reciting 'chlorine,' because the former is broader than the latter.").

[35] Interestingly, Amgen did not include the word "human" in the actual third preliminary amendment. Amgen claims it did not do so because it was "superfluous" with the portion of the amendment that referred to the sequence of Figure 6. Amgen's Reply Mem. [Doc. No. 733] at 8. In other words, Figure 6—which contains 166 amino acids—sufficiently signified human EPO (as opposed to non-human). This, however, is extrinsic evidence to which the Court cannot resort in analyzing this criterion.

[36] The exact remarks are:

> Applicant notes that [the amended '080 claims] all differ in scope from glycoprotein claim 1 of [the '933 patent] in specifying that the claimed subject matter comprises the mature human erythropoietin sequence of Figure 6. [Claim 1 of the '080], (like glycoprotein claim 1 [of the '933 patent]), recites carbohydrate differences in compari-

differentiating its product from prior art based on the Figure 6 limitation but instead based on glycosylation and source limitations. This comports with the state of the art at the time. There was no prior art disclosing a 1-165 sequence for human EPO and thus Amgen had no need to distinguish its claims over any such equivalent. To the extent that it needed to distinguish prior-art human urinary EPO, Amgen did so by including the limitations noted above regarding differences in glycosylation and isolation from human urine.

Further, Amgen points out that at the time this amendment was made, Amgen had already disclosed to the Patent Office the reference that reveals that human EPO is missing the COOH-terminal Arg 166 amino acid residue. Amgen's Post-Hr'g Mem. at 11; Second Preliminary Amendment, Trial Ex. 3, Tab 3 at 140 (disclosing to the Patent Office that the 166 arginine cleaved off by referencing Recny).[37] Given that Amgen and the Patent Office knew that human EPO (and, therefore, example 10 of the '080 patent) actually had a 1-165 amino acid sequence, a "reasonable inference" is that the amendment was not made to surrender human EPO with a 1-165 amino acid sequence or distinguish 1-166 from 1-165 because that would have illogically resulted in either Amgen surrendering its preferred embodiment or pursuing a patent that it and the Patent Office knew to be incorrect. *Festo II*, 535 U.S. at 724 (noting that the purpose of applying estoppel

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> son to human urinary [EPO] and claim [2] recites a negative limitation with respect to isolation from human urine.

Id.

[37] Recny refers to the article that reveals that the urinary hormone is missing the COOH-terminal Arg 166 amino acid residue. Recny, et al., *Structural Characterization of Natural Human Urinary and Recombinant DNA-derived Erythropoietin*, J. Biol. Chem., 262(35), 17156-63 (Dec. 15, 1987). This reference is cited in the '080 patent disclosure as one that was reviewed by the Examiner. Amgen's Post-Hr'g Mem. at 11; Trial Ex. 3 ('080 Patent), TKT/HMR's App., Tab A.

is "to hold the inventor to the representations made during the application process and the inferences that may *reasonably* be drawn from the amendment") (emphasis added).[38] To infer such a chain of events would not be reasonable.

TKT/HMR counters, in essence, with the argument that all of this history is irrelevant. It contends that *any* amendment made to avoid double patenting *cannot* be tangential "because it goes to the heart of the reasons why the claims were ultimately allowed." TKT/HMR's Post-Hr'g Mem. at 35. This argument fails, however, because it conflates the inquiry regarding whether the amendment was made for patentability reasons, that is, whether the presumption of prosecution history estoppel applies in the first place, with the inquiry into the rationale for the amendment at hand. The rationale cannot be more than tangentially related to the equivalent in question—but it can be more than tangentially related to patentability issues—if this were not so, this tangentiality standard would be circular and insurmountable because prosecution history estoppel applies when a narrowing amendment is made for patentability reasons. If HMR/TKT's interpretation were correct, arguably the Supreme Court would not have

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[38] This reasonable inference—that the amendment was not made to differentiate a 165 amino acid EPO from a 166 amino acid EPO—would not *alone* be sufficient to overcome the presumption. Although one scholar deems the tangential standard met when the patentee proves there is no objective intent to disclaim, *see* J. Jason Lang, *The German Resolution: A Proposed Doctrine of Equivalents Analysis and a Flexible Rule of Prosecution History Estoppel For Biotechnology*, 52 Emory L.J. 427, 478 (2003), upon close reading of *Festo II*, it appears such proof is not enough. The prosecution history must affirmatively show that the purpose of the amendment was no more than tangentially related to the equivalent in question—not just a lack of intent to surrender territory. Here, however, proof of lack of intent to surrender is not the only proof supporting Amgen's contentions. As discussed earlier, the prosecution history also affirmatively supports that the purpose of the amendment was unrelated to the equivalent in question.

held that tangentiality was one way of overcoming the "presumption;" and the Federal Circuit, which agreed with this Court that the amendment was made for patentability reasons, *Amgen II*, 314 F.3d at 1345, would likely have noted on remand that, of the potential ways to rebut the "presumption," tangentiality was foreclosed.

In sum, Amgen has shown by a fair preponderance of the evidence that the amendment at issue was made for a reason only tangentially related to the equivalent in question. Therefore, the Court holds that Amgen has satisfied the "tangential" criterion as defined by the Federal Circuit in *Festo III*.[39]

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[39] As suggested earlier, the Court reaches this conclusion because the Federal Circuit's *Festo III* decision directs the Court to conduct its analysis based only on intrinsic evidence. Had the Federal Circuit interpreted the Supreme Court's decision to allow for resort to extrinsic evidence—as this Court so interpreted the decision—Amgen would not have prevailed with respect to this criterion. Two pieces of extrinsic evidence—ironically submitted by Amgen itself—demonstrate that the amendment was indeed more than tangentially related to the equivalent in question.

1) *Admissions by Amgen's Counsel*

Amgen's counsel stated repeatedly at the July 28, 2003 motion hearing that the purpose of the amendment was not only to limit the EPO claimed in '080 to human (as opposed to human and non-human) but to specify a sequence. "[W]e wanted claims that limited the invention to the sequence so that it specified the sequence of the protein." 7/28/2003 Mot. Hr'g Tr. at 72, ll. 24-25. "The amendment was made *to distinguish claims that had no sequence* and embraced EPOs of multiple species *to claim a protein that has the human sequence*." *Id.* at 73, ll. 14-16 (emphasis added). Although it is likely that Amgen wanted to specify a sequence to avoid potential objections related to the strict enablement and written description requirements of patent law, *see* Lang, *supra*, at 464 (stating that "[t]he strict enablement and written description requirements often limit claiming of biotechnological inventions to specific DNA and amino acid sequences"), such a rationale does not negate Amgen's admissions. Notwithstanding any ulterior motive for submitting the amendment, by stating that it wanted specifically to claim a sequence, Amgen admits that at least part of the amendment's rationale was more than tangentially related to

any human amino-acid sequence including a 1-165 amino acid sequence, the equivalent in question.

An analogy is appropriate here. Suppose a patentee described, in an amendment, a four-cornered object in detail that *happened* to depict a square. The patentee may be able to prove that the rationale for the amendment was not related to the shape of the object and, therefore, was not related to an equivalent that specifically claimed a rectangular shape. An assertion by the patentee to the Court, however, that it made the amendment to specify a particular shape suggests that the amendment indeed would be more than tangentially related to the equivalent that depicted a rectangle. *Cf. Bosch*, 223 F. Supp. 2d at 1171 (noting that "a strong argument can be made that the reason JSB used the phrase 'in a semicircle' was to convey that the lever goes around the internal gear, not to convey that the lever must be of a particular shape"). The same logic holds true here, especially when considered in conjunction with another submission by Amgen that is discussed below.

2) *Expert Testimony Regarding Interpretation of the Amendment and Amgen's Intentions*

Amgen asserts and supports with expert testimony that Amgen intended and those skilled in the art interpreted its amendment to cover human urinary EPO with a 165 amino acid sequence. Amgen plainly stated that it "intended the sequence limitation to cover human EPO compositions having the 1-165 amino acid sequence." Amgen's Post-Hr'g Mem. at 2; *see also* Amgen's Mem. in Support at 6-10. While a patentee's subjective intent ought not be considered by the Court when unsupported by the prosecution history, *Vitronics*, 90 F.3d at 1584, this intent is supported by the file wrapper. Amgen disclosed to the Patent Office the reference that reveals that human EPO—Example 10 of the '080 patent—has 165 amino acids; and Amgen explained to the Patent Office that other limitations in the '080 claims—not the Figure 6 limitation—distinguished its claimed EPO from all other human urinary EPO. Third Preliminary Amendment, Trial Ex. 2005, TKT/HMR's App., Tab E at 9. These two pieces of prosecution history support Amgen's assertion that it wrote the amendment *in order to cover* the recently discovered human EPO with a 165 amino acid sequence and that the Patent Office believed that this amendment so covered it. If the Patent Office did not believe this, it arguably would not have allowed the amendment for it would have made the patent specification incorrect because the patent specification included Example 10, then understood to result in an EPO with a 165 amino acid sequence.

4. Some Other Reason?

As discussed above, the Federal Circuit stated that the third criterion should be a narrow one and that courts should consider only the prosecution history record "[w]hen at all possible" in conducting its analysis. *Festo III*, 2003 WL 22220526, at *6. That being said, the Court did not detail an exhaustive list of the type of circumstances that satisfy the criterion or decide when resort to extrinsic evidence would be deemed necessary. Nor did it describe "what evidence outside the prosecution history record, if any, should be considered in determining if a patentee has met its burden under this third rebuttal criterion." *Festo III*, 2003 WL 22220526, at *6. Therefore, the boundaries of analysis under this criterion will be refined by courts, such as this one, faithfully interpreting *Festo II*, *Festo III*, and any future relevant decisions by the Supreme Court and the Federal Circuit.

In further support, an expert (and also the author of the amendment) testified that the claim "would cover . . . 166, 165, whatever the process format is in the particular [host] cell." Borun Trial Test., Amgen's App., Tab D at 2884-85. This testimony supports Amgen's contention regarding its intent and that those skilled in the art would have interpreted the amendment to cover human EPO with a 165 amino acid sequence.

While all of the intrinsic evidence shows by a fair preponderance that the purpose of the amendment was *not* to *differentiate* human EPO with 166 amino acids from human EPO with 165 amino acids (as discussed earlier), when considered in combination with the extrinsic evidence, it shows at least part of the rationale underlying the amendment was to depict a sequence that covered the recently discovered human urinary EPO with 165 amino acids. As such, the rationale would be more than tangentially related to the equivalent in question. Although the amendment may have been specifically designed to avoid double patenting by claiming human EPO, it was also specifically designed to cover human urinary EPO, which was then known by Amgen, the Patent Office and those skilled in the art to have the 1-165 amino acid sequence. Thus, when considering the intrinsic *and* extrinsic evidence, it is apparent that the amendment is more than peripherally related to the "insubstantial substitute," human urinary EPO with 165 amino acids.

While resort to extrinsic evidence will not always be necessary to determine if this third criterion has been met, objectively determining whether "some other reason" reasonably prevented the patentee from describing the alleged equivalent in its narrowed claim, may—like the foreseeability analysis—"depend on underlying factual issues relating to . . . the state of the art and the understanding of a hypothetical person of ordinary skill in the art at the time of the amendment." *Id.* at *5. This is so even if the "other reason" is the shortcomings of language—the one reason the Federal Circuit suggested would meet this criterion—because, without a thorough understanding of the state of the technology and how certain language would be interpreted by one skilled in the art at the time of the amendment, the Court would not be able to determine if adequate language existed that should have been used by the patentee.

While it is true that courts regularly—and in fact ought—construe claims without resort to expert testimony regarding how one skilled in the art would interpret the claims, a court's claim construction often narrows the claim in a way that may have been unintended by the patentee. Such narrowing is the reason why the doctrine of equivalents was created—to capture, despite the inadequacies of language, the essence of the invention in light of technological advances. *See generally Festo II*, 535 U.S. at 731-32; *Graver Tank*, 339 U.S. at 607; *Autorigo Co.*, 384 F.2d at 397. Undeniably, there is a difference between how a court approaches claim construction and how it approaches the doctrine of equivalents and prosecution history estoppel. The policy of avoiding all extrinsic evidence except when necessary in claim construction is to ensure that a court is determining solely the literal terms of the claim, that is, those claims of which the public was notified. The policy behind the doctrine of equivalents, on the other hand, is more equitable in nature; it seeks to determine what the patentee was surrendering and any "reasonable inferences" that can be drawn from the patentee's

representations. *Festo II*, 535 U.S. at 737-39; see also *Festo III*, 2003 WL 22220526, at *4 ("Prosecution history estoppel has traditionally been viewed as equitable in nature, its application being 'guided by equitable and public policy principles.'") (citations omitted). Thus, reasonableness, although not a part of claim construction, is central to the doctrine of equivalents.

The idea of reasonableness was reinforced by the Supreme Court in *Festo II*. It held, generally, that to rebut the presumption of surrender "the patentee must show that at the time of the amendment one skilled in the art could not *reasonably be expected* to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo II*, 535 U.S. at 741 (emphasis added). Moreover, the Supreme Court also specifically included an analysis of reasonable expectations of the patentee in the third criterion to rebut the presumption. *Id.* Thus, the Court's analysis at this stage—as opposed to that during claim construction—includes a reasonableness inquiry that involves questions of equity, even after *Festo II*.

The reasonableness inquiry as defined by *Festo II*, however, is now different than it used to be. Before *Festo II*, the reach of prosecution history estoppel was decided by considering what a competitor or one skilled in the art reasonably would have determined was surrendered by the amendment. *Modine Mfg. Co.* v. *U.S. Intn'l Trade Comm'n*, 75 F.3d 1545, 1555 (Fed. Cir. 1994); *Zenith Labs.* v. *Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1424 (Fed. Cir. 1994); *Hoganas AB* v. *Dresser Indus., Inc.*, 9 F.3d 948, 952 & n.15 (Fed. Cir. 1993); *Haynes Intn'l, Inc.* v. *Jessup Steel Co.*, 8 F.3d 1573, 1578 & n.4 (Fed. Cir. 1993). After *Festo II*, however, the focus is not on what those skilled in the art reasonably would have concluded was relinquished but on what subject matter the patentee itself reasonably should have included in the amendment. *Leading Cases*, *supra*, at 409 ("The Court's new

test shifts the estoppel inquiry from the ex post perspective of a reasonable competitor to the ex ante perspective of the person drafting the patent."); Golian, *supra*, at 599. Under the pre-*Festo II* approach, a patentee could expect to retain all but those equivalents surrendered in the amendment. Now, the patentee is on notice that all equivalents that reasonably could be expected to be included are surrendered. In other words, a patentee survives prosecution history estoppel if it can show that drafting the claim to include the equivalent was not a reasonable expectation. Thus, even after *Festo II*, when analyzing the third criterion, the Court must make a reasonableness inquiry, but now it must ask what a reasonable patentee *could be expected* to have done. *See, e.g.*, Fu, *supra*, at 137 (noting that *Festo II* includes a reasonableness test, that is, an equitable consideration). This reasonableness inquiry requires the Court to look into the circumstances and in some cases, like the one at hand, to consider extrinsic evidence.

Amgen's main argument under this third rebuttal criterion is that it could not reasonably be expected to have described the equivalent in question because competitors and those skilled in the art would have interpreted the amendment, at the time it was made, actually to cover the equivalent. In support, Amgen submits extrinsic evidence in the form of expert testimony, suggesting that the drafter of the amendment in question—and those skilled in the art—interpreted the amendment to cover all human EPO whether it had 165 amino acids or 166. Borun Trial Test., Amgen's App., Tab D at 2885.[40]

There is also intrinsic evidence supporting this position. As explained earlier, the prosecution history shows that the

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[40] The drafter is one skilled in the art. The fact that he interpreted the amendment in this way supports the contention that others skilled in the art would have interpreted the amendment similarly.

Patent Office Examiner was informed by Amgen that human urinary EPO, such as that produced by the preferred embodiment depicted in Example 10, has the 1-165 amino acid sequence of Figure 6. Recny, *supra*, Trial Ex. 53 at 17156; Amgen's Post-Hr'g Mem. in Support at 11. In other words, the Patent Office examiner had the information that human urinary EPO has the exact amino acid sequence shown in Figure 6, except for the 166th arginine. Moreover, the reference that discloses how the 166th arginine is cleaved off was revealed to the Patent Office during the prosecution and cited as a reference in the '080 patent disclosure. Trial Ex. 3 ('080 Patent), TKT/HMR's App., Tab A at 8; Amgen's Post-Hr'g Mem. in Support at 11 n.26. Thus, given Example 10, either the Patent Office was knowingly enabling the prosecution of an incorrect patent, or it too interpreted the amendment to cover human urinary EPO with a 1-165 amino acid sequence.[41]

Overall then, the evidence supports the contention that Amgen, the Patent Office, and, importantly, those skilled in the art interpreted the claims as amended literally to encompass the particular equivalent in question here, an EPO with a 165 amino acid sequence.

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[41] Without Example 10, the fact that Amgen was claiming human EPO with 166 amino acids would not itself have been incorrect because, at the time of the amendment, it was not known that *no* human EPO comprising 166 amino acids existed. According to counsel, at that time there were "reports in the literature that there are expressed by certain cells 166 forms of EPO and there are expressed by other cells 165." 7/31/03 Mot. Hr'g Tr. at 77, ll. 23-25, and 78, l. 1. In other words "what was known was the gene sequence for human EPO encoded 166 amino acids" and "when that gene sequence is put in certain cells it gets 165. For example, when it was put in the CHO cells in Example 10 of Lin's patent it produced 165." *Id.* at 78, ll. 11-16. To this day, it is actually unknown whether there is a human EPO with 166 amino acids. *Id.* at ll. 3-4. "EPO has never been purified from human blood. It is so vanishingly small, no one has ever gotten to its actual human form." *Id.* at ll. 6-8.

While the correct inquiry, after *Festo II*, is not what those skilled in the art or a reasonable competitor would conclude was surrendered by the amendment, a competitor's reasonable interpretation of the amendment is necessarily relevant in determining what the patentee reasonably can be expected to have drafted.[42] Claims are drafted for a particular audience—those skilled in the art. Given that there is evidence that those skilled in the art would have interpreted the amendment to include human EPO with a 165 amino acid sequence—the equivalent in question—it would not be reasonable to expect Amgen to have drafted the claim differently. While the Court did indeed construe the claim differently,[43] such construction should not prevent the Court from resorting to this extrinsic evidence—evidence it did not consider during claim construction[44]—to understand what can be reasonably expected of the patentee. While such extrinsic evidence may be inappropriate in claim construction, as discussed earlier, it

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[42] In *Haynes*, the Federal Circuit recognized that the vantage point of one skilled in the art is consistent with the vantage point of a reasonable competitor. *Haynes*, 8 F.3d at 1578 n.4.

[43] As mentioned, *supra*, in *Amgen I*, Amgen argued that the amendment should be construed to mean "the fully processed form of the protein secreted by a cell . . . when it transcribes and translates the DNA in Figure 6." *Amgen I*, 126 F. Supp. 2d at 86. TKT/HMR contended that the phrase means "the 166 amino acid sequence of human EPO shown in Fig. 6." *Id.* The Court agreed that the term "mature" meant the fully processed form of EPO secreted by the cell, *id.*, but found that the Figure 6 limitation limited the meaning of the claim terms to the entire 166 amino acid sequence disclosed in the figure. *Id.* at 100.

[44] The record indicates that the Court did not rely on extrinsic evidence to construe the claim. *Amgen I*, 126 F. Supp. 2d at 86, n.12 (noting that the Court did not receive evidence during the *Markman* hearing); *see also, Amgen I*, 126 F. Supp. 2d at 81 (commenting on the importance of separating claim construction from issues of infringement to avoid conflating fact and law and noting that during the *Markman* hearing the Court considered counsel's arguments relating to the specification and prosecution history but that "evidence was neither offered nor admitted").

appropriately is considered in the context of this criterion's reasonableness inquiry.

It is this part of the criterion, the reasonableness element, that TKT/HMR completely ignores and that is determinative here. TKT/HMR focuses its counter-argument on what Amgen, the patentee, *could have* drafted. TKT/HMR argues, as it did under the foreseeability prong, that Amgen could have easily drafted a claim that literally encompassed the equivalent. While the Court finds this assertion to be true, as discussed *supra*, Amgen has shown by a fair preponderance of the evidence that those skilled in the art (and the Patent Office) interpreted the amendment to encompass the equivalent.[45] The fact that the Court later determined—under a pre-*Festo II* analytic framework—that this amendment did not encompass all theoretically possible human EPO does not justify holding Amgen to the literal terms of the amended claim. The Supreme Court made clear that *Festo II* does not go that far and that, if it did, it would defeat the purpose of the doctrine of equivalents:

> The amendment does not show that the inventor suddenly had more foresight in drafting of claims than the inventor whose application was granted without amendments having been submitted. It shows only that he was familiar with the broader text and with the difference between the two. As a result there is no more reason for holding the patentee to the literal terms of an amended claim than there is for abolishing the doctrine of equivalents altogether and holding the patentee to the literal terms of the patent.

Festo II, 535 U.S. at 738. Here, the evidence shows that Amgen was familiar with the broader text, human *and* non-

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[45] Importantly, TKT/HMR has not produced any evidence that those skilled in the art interpret the claim differently. In fact, all of the evidence supports Amgen's contentions. Thus, under the preponderance of the evidence hurtle, Amgen has met its burden.

human. It amended its claims to specify human EPO and believed that its patent and this amendment encompassed the alleged equivalent. It is not reasonable to expect one skilled in the art to have used different claim language when the language that was used was interpreted by those skilled in the art to be sufficiently descriptive.[46] This is just the sort of "shortcoming[] of language" or "linguistic" limitation to which the Federal Circuit referred in its opinion. *Festo III*, 2003 WL 22220526, at *6, *8. Here, the amendment made clear that the patent did not cover nonhuman but failed (according to the Court's claim construction) to make clear that it covered human EPO with a 165 amino acid sequence. While this drafting error was fatal to Amgen's literal infringement argument, it is not fatal to Amgen's ability to rebut the "presumption" under this prong of the analysis. As the Supreme Court explained, "language is an imperfect fit for invention," the "narrowing amendment may demonstrate what the claim is not; but it may still fail to capture precisely what the claim is." *Festo II*, 535 U.S. at 739; Lang, *supra*, at 478-86 (commenting that language limitations or an art's unpredictability should work to overcome the presumption.) A patentee should not be able to attain through litigation that

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[46] Furthermore, it is clear from the record that claiming any amino acid sequence 165 or 166 is like claiming a moving target. No one knows what is really expressed in humans because, as Amgen's counsel explained, "EPO has never been purified from human blood. It is so vanishingly small, no one has ever gotten to its actual human form." 7/31/03 Mot. Hr'g Tr. at 78, ll. 6-8. To that end, biotechnology is itself an "unpredictable technology." Lang, *supra*, at 457. This unpredictability impairs a patentee's ability to draft claims to cover the full scope of the patent because the art "generally offer[s] only a handful of linguistic tools for circumscribing an invention." *Id.* at 477, 485 ("The unpredictability of this art alone should rebut the presumption of prosecution history estoppel."); Borun Trial Test., Amgen's App., Tab D at 2884-85 (explaining that after it became known that the 166th amino acid was chopped off, the Genetic Institute and others challenged the conclusion that a CHO cell product terminates with the 165th amino acid).

which was surrendered during the prosecution history. Here, however, Amgen has shown by a fair preponderance of the evidence that, while the amendment failed to capture precisely what the claim is, the 165 amino acid equivalent was not surrendered.

Although this analysis is not directly contrary to the holdings of *Festo III*, the Federal Circuit strongly indicated that it will—when the issue is ripe before it—cabin in the third criterion with respect to the use of extrinsic evidence and the circumstances that satisfy the criterion. Thus, this Court rests its decision on the tangential criterion but holds in the alternative that Amgen has also met the third criterion, that is, Amgen has shown by a fair preponderance of the evidence that some other reason exists that suggests that at the time of the amendment it could not *reasonably* be expected to have drafted the claim to describe the insubstantial substitute in question.

III. CONCLUSION

In light of the Federal Circuit's narrow interpretation of the third criterion and admonition to rely only on intrinsic evidence whenever possible, the Court's analysis under the "some other reason" category and its resort to extrinsic evidence is less certain. Ironically, however, the "tangential" criterion—originally rejected on the basis of extrinsic evidence—is now persuasive once the focus narrows to the prosecution history alone. Frankly, a holding based on the "tangential" criterion seems less satisfactory and more artificial than the Court's original holding based on "some other reason," yet I deem it compelled by the Federal Circuit's less than generous reading of the Supreme Court's decision in *Festo II*. Perhaps the disjunction I perceive arises from the incredibly complex nature of recombinant DNA technology compared to the mechanical technology present in the *Festo* line of cases. Future decisions will doubtless refine

these matters. In any event, either way Amgen "wins," that is, rebuts the presumption of prosecution history estoppel.

Accordingly, upon further consideration in light of *Festo III*, HMR/TKT's motion for judgment that Amgen is estopped from asserting equivalent infringement of the '080 patent [Doc. No. 678] is DENIED and Amgen's motion for judgment that claims 2-4 of the '080 are infringed under the Doctrine of Equivalents [Doc. No. 659] is ALLOWED.

SO ORDERED.

/s/ William G. Young
WILLIAM G. YOUNG
CHIEF JUDGE